REVIEW ARTICLE

Mendelian cytogenetics. Chromosome rearrangements associated with mendelian disorders

Niels Tommerup

The first successful mapping of a mendelian disorder by chromosome rearrangements was that of the Duchenne muscular dystrophy locus to Xp21.[1–5] Since then, chromosome aberrations which delete, truncate, or otherwise rearrange and mutate specific genes have not only helped in the mapping of other disease loci,[6] but have turned out to be key elements for the rapid isolation of disease genes by positional cloning strategies.[7] Accordingly, a listing of the clinical disorders in which associated chromosome rearrangements have been described forms a part of the Human Gene Mapping Workshops.[6] Although the early success led to a proposal for systematic cytogenetic analysis of subjects with mendelian disorders,[8] this has rarely been done. A common feeling is that, as mutations, these rearrangements are rare exceptions. The aim of the present review is to document that they may be rare, but are not exceptions, and to focus on factors which may influence their occurrence and facilitate their detection.

Contiguous gene syndromes in relation to mendelian genetics

Genetic disorders are usually classified into mendelian, chromosomal, and multifactorial categories. Mendelism involves transmission patterns of traits which traditionally are thought to be determined by single genes. The mere fact that a chromosome rearrangement may lead to the development of a mendelian disorder suggests that this distinction between mendelian and chromosome disorders may be arbitrary.[9] This is illustrated by Miller–Dieker syndrome (MDCR), lissencephaly with a characteristic facial appearance, that was originally listed as an autosomal recessive condition owing to the presence of familial cases with two or more affected sibs.[9] All familial cases analysed have so far been shown to be associated with unbalanced segregation of familial translocations or inversions, leading to segmental aneuploidy (deletion) of a distal segment of 17p.[10–12] Thus, MDCR not associated with a chromosome abnormality is probably best explained as an autosomal dominant condition where all mutations are de novo.

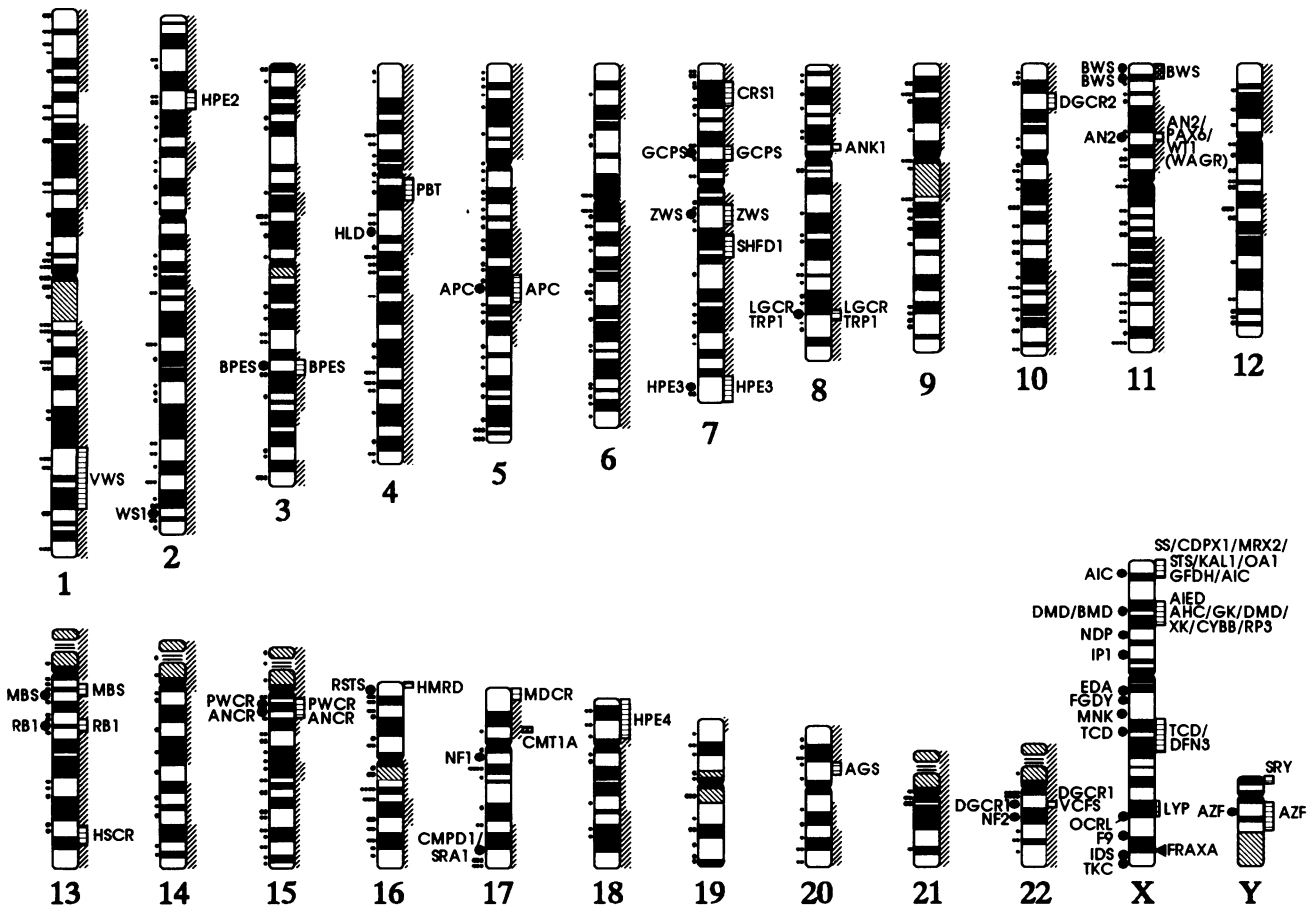
MDCR also illustrates a mutational mechanism that may eventually explain a substantial part of the heterogeneity and overlap in syndromology: contiguous gene syndromes where microscopic or submicroscopic deletions (or duplications) involve an array of closely positioned genes.[13,14] A purpose of the molecular characterisation of contiguous gene syndromes is to identify individual genes responsible for specific components of the phenotypic complex. This is probably best illustrated by the molecular studies of deletions and translocations involving 11p13 associated with various combinations of Wilms's tumour, aniridia, genitourinary malformations, and mental retardation (WAGR complex).[15] The resulting isolation of candidate genes for Wilms's tumour (WT1)[16,17] and aniridia (AN2, PAX6)[18,19] now provides a means for molecular studies and delineation of monogenic conditions within 11p13.[20–24] Similarly, the dissection of the phenotype in MDCR has begun with the demonstration of submicroscopic deletions in cases with isolated lissencephaly.[25,26]

Any visible chromosome imbalance almost invariably represents a contiguous gene disorder, but few chromosomal syndromes include features of sufficient specificity to permit a correlation with a recognised mendelian disorder. This includes many of the classical chromosome disorders,[27] as well as newly recognised ones.[28] Although these chromosome aberrations may not have immediate implications for known mendelian traits, future molecular dissection of these disorders may change this.

Chromosome rearrangements in relation to autosomal dominant, autosomal recessive, and X linked disease

Specific chromosome rearrangements have predominantly been described in autosomal dominant (AD) and in X linked conditions. Of the 625 chromosomally mapped loci associated with genetic disorders, 54 (8·6%) are X linked.[29] However, more than one third of the approximately 70 mendelian disorders associated with a specific chromosome rearrangement are X linked[6] (figure). This excess can be explained by almost routine application of cytogenetic analysis in two particular groups of

The Danish Centre for Human Genome Research, The John F Kennedy Institute, Gl Landevej 7, DK-2600 Glostrup, Denmark, and Department of Medical Genetics, Ullevaal University Hospital, Oslo, Norway.
N Tommerup



Deletion Duplication Locus specific rearrangement (translocation, inversion)

Fragile site Regions where viable deletions have been described.

Regions with only 1–3 reports of viable deletions.

Translocation breakpoints detected in a non-biased way in prenatal diagnosis[79]

Localisation of mendelian disorders where chromosome rearrangements have been described. For explanation of symbols, see Appendix.

patients: females affected with X linked diseases, suggesting X;autosome translocations, and males suffering from two or more X linked disorders, suggesting a contiguous gene syndrome. Since there are no a priori reasons to believe that chromosome rearrangements should be less frequent in AD than in X linked disorders, the underrepresentation in AD disorders is probably because of ascertainment bias.

The cytogenetic data in autosomal recessive (AR) disorders are so scanty that reliable statements regarding their frequency cannot be made. In only one AR disorder (Zellweger syndrome) has more than one chromosome rearrangement been described, a de novo deletion and a de novo inversion.[30 31] A specific chromosome mutation will only show an AR locus if the other allele happens to be mutated (unmasking of heterozygosity),[32] and this will be a rare occurrence as the gene frequencies for even the most common AR disorders do not exceed 1/25 to 1/50. Owing to the number of recessive traits, and the relatively high frequency of familial translocations and inversions in man,[33] some of these breakpoints may affect recessive loci. Thus, several murine balanced translocations are lethal in the homozygous state.[34] The risk of unmasking of heterozygosity by a transmissible chromosome rearrangement will increase with the number of individuals that receive the rearrangement. In addition, familial translocations may predispose to the formation of uniparental

Table 1 Chromosome rearrangements in deletion viable regions.

Disorder (locus symbol)	Chromosomal localisation	Type of rearrangement	
		Deletions (No)	Locus specific type
AGS	20p11.23–12.1	Multiple[178b 179a]	
AHC	Xp21	Multiple[72 180a]	
AIC	Xp22.3	Multiple[70 181a]	t(X;3)(p22;q12)[182a]
AIED	Xp21	1[180a]	
ANCR	15q11–12	Multiple(mat)[65–68a,d 122a 183a]	inv(15)(p11q13)mat[68 69b]
AN2/PAX6	11p13	Multiple[52a,d 54d]	t(4;11)(q22;p13)[60b]
			t(11;22)(p13;q12.2)[58b]
			t(5;11)(q13.1;p13)[59b]
			t(5;11)(q11;p13)[284ax]
ANK1	8p11.1	3[187a 188a 186c?]	t(8;12)(p11;p13)[184b]
			t(3;8)(p21;p11)[185b]
APC	5q22	5[189a 191a 190b 183d]	t(5;10)(q22;?)[e]
AZF	Yq11	Multiple[193–196a]	
BPES	3q23	4[199a 172d]	t(3;11)(q21;q23)[198b]
			t(3;4)(q23;p15.2)[200a]
			t(3;8)(q23;p21.1)[197a]
CDPX1	Xp22.3	Multiple[70]	
CRS1	7p21	Multiple[207 208a]	
CYBB	Xp21	Multiple[72 209 210a,b]	
DFN3	Xq21	Multiple[37 211]	
DGCR1	22q11	Multiple[213–217a,d]	t(2;22)(q14.1;q11.1)[212b]
DGCR2	10p13	7[214a,d 218a]	
DMD/BMD	Xp21	Multiple[71 72a,b]	Multiple[219a]
GCPS	7p13	3[163a 164a]	t(3;7)(p21.1p13)[160b]
			t(6;7)(q27;p13)[161b]
			t(6;7)(q12;p13)[162]
GK	Xp21	Multiple[71 72a,b]	
HLD	4q12		t(4;5)(q21;p15.3)[231b]
			t(4;6)(q21;p24)[232b]
HMRD	16p13.3	4[88a,d]	
HPE2	2p21	4[233a]	
HPE3	7q35	Multiple[234 236 237a,d]	t(7;9)(q36;q34)[235b]
HPE4	18p	Multiple[234 238a,d]	
HSCR	13q33.1	3[239–241a]	
KAL1	Xp22.3	Multiple[70a]	
LGCR	8q24.11	Multiple[127 244 245 248a,d]	t(2;8)(q33;q24.1)[127]
			t(4;8)(p15.3;q24.1)[127]
			t(8;11)(q24.11;p15.5)[246]
			inv(8)(q11.23q21.1)[247b]
LYP	Xq25	1[73b]	
MBS	13q12.2	1[249a]	t(1;13)(p34;q13)[250b]
MDCR	17p13	Multiple[10–12 25 26a,d]	
MRX2	Xp22.3	Multiple[70]	
NF2	22q12.2?		t(4;22)(q12;q12.2)[254b]
OA1	Xp22.3	Multiple?[70]	
PBT	4q12–13	3[257 259 260a]	t(4;15)(q12q21;q11)[258ax]
PWCR	15q11–12	Multiple(pat)[48–51a,d]	1 X;A translocation (see ref 61)[a]
			5 autosomal translocations[61b]
			inv(15)(p13q13)pat[64]
RB1	13q14	Multiple[38–44a,b,c?,d]	Multiple[41]
SHFD1	7q11.2–21.3	7[264 265a]	t(5;7;9)(q11.2q34;q21.2q31.3;q22.1)[266a]
			t(7;9)(q11.21;p12)[263b]
SRY	Yp12	Multiple[70a 267 268a]	
SS	Xp22.3	Multiple[70a]	
STS	Xp22.3	Multiple[70a]	
TCD	Xq21	Multiple[37 174b 271a,b]	t(X;7)(q21.2;p14)[272a]
			t(X;13)(q21.2;p12)[274a]
TKC	Xq28		t(X;3)(q28;q21)[275a]
			t(X;10)(q28;q11.2)[275a]
TRP1	8q24.11	5[276–280a,c]	dir ins(8)(q24.11q13.3q21.13)[281b]
VCFS	22q11.2	Multiple[282 283a,d]	
VWS	1q32–41	1[285a]	
WS1	2q35		inv(2)(q35q37.3)[287a]
WT1	11p13	Multiple[52a,b,d]	
ZWS	7q11.23	1[30a]	inv(7)(p12q11.23)[31a]

See Appendix for explanation of locus symbols. a = de novo aberration. b = familial transmission. c = evidence of germline mosaicism. d = unbalanced familial reciprocal translocation/inversion. e = Meera-Khan, personal communication. x = visibly unbalanced translocation.

disomy, whereby AR mutations can be reduced to homozygosity.[35] The occasional occurrence of an inherited balanced translocation or inversion would therefore not be unexpected in AR disorders.[36]

The effect of chromosome localisation on types and frequencies of chromosome rearrangements

Exact determination of frequencies of chromosome rearrangements in mendelian disorders can only be made by systematic studies of specific mendelian disorders. This has only been done in a few disorders, retinoblastoma (RB1) being the classical one. The results from RB1 may not necessarily be valid for other disorders, and one factor that will influence the frequency of chromosome rearrangements in a specific disorder is the chromosomal localisation of the corresponding gene.

Visible deletions among liveborns are absent or extremely rare for several regions of the human genome (figure),[27] probably because they are incompatible with fetal survival.[37] Whereas deletions are the most frequent type of rearrangement in those disorders which map to the 'deletion viable' regions (table 1, figure), visible deletions do not occur in liveborns affected with mendelian disorders mapping to the 'deletion non-viable' regions (table 2). The division of the genome into a deletion viable and non-viable part may have consequences not only for the type and fre-

Table 2 Chromosome rearrangements in deletion non-viable regions.*

Disorder (locus symbol)	Chromosomal localisation	Type of rearrangement	
		Miscellaneous	Locus specific type
BWS	11p15.4–15.5	del(11)(p11p13)[203a]†	t(9;11)(p11.11p15.5)mat[103b]‡
		del(11)(p11p13)[205a]†	t(4;11)(p15.2;p15.4)mat[103b]
		multiple dup(11p)pat[103 202d]	t(11;22)(p15.5;q12)mat[204b]
			t(11;16)(p15.5;q12)mat[103b]
			t(11;12)(p15.5;q13.1)mat[103b]
			inv(11)(p11.2p15)mat[126b]
			inv(11)(p15.4q22.3)mat[103b]
CMPD1	17q24.3–25.1		46,XX,t(1;17)(q42.1;q25)[95a]
			46,XX,inv(17)(q12q25)[96a]
CMPD1/ SRA1	17q24.3–25.1		46XY,t(2;17)(q35;q23–24)[97a]
			46,XY,t(7;17)(q34;q25)[95a]
			46,XY,t(13;17)(q31;q25)[95a]
EDA	Xq13.1		t(X;9)(q13.1;p24)[225 228a]
			t(X;12)(q13.1;q24.2)[227a]
			t(X;1)(q13.1;p36.33)[224a]
F9	Xq27		t(X;1)(q27;q23)[229a]
FGDY	Xq13		t(X;8)(q13;p21.2)[118b]
IDS	Xq28		t(X;5)(q27;q31)[243a]
IP1	Xp11		t(X;15)(p11;q11) or (q11;p11)[142a]
			t(X;9)(p11;q34)[143a]
			t(X;17)(p11;p11.2)[145a]
			t(X;9)(p11;q33.2)[145a]
			t(X;13)(p11.21;q12.3)[144a]
			t(X;10)(p11;q22)[146a]
			t(X;4)(q21;q28)[9]
			t(X;5)(p11.2;q35.2)[147a]
			45,X/46,Xr(X)[141a]
MNK	Xq13.3		t(X;2)(q13.3;q32.2)[117a]
			t(X;1)(q13.3;q21)§[a]
			ins(X)(p11.4q13.3q21.2)mat[106b]
NDP	Xp11		t(X;10)(p11;p14)[253a]
			inv(X)(p11.4q22)[254b]
NF1	17q11.2		t(1;17)(p34.3;q11.2)[92b]
			t(17;22)(q11.2;q11.2)[93b]
		+?r(17)(cen-q12), del(17)(cen-q12)[91]	
OCRL	Xq26.1?		t(X;3)(q25;q27)[256a]
			t(X;20)(q26.1;q11.2)[257a]
RSTS	16p13.3		t(2;16)(p13.3;p13.3)[84a]
			t(7;16)(q34;p13.3)[85a]
			t(16;22)(p13.3;?)‖
			inv(16)(p13.3;q13)[86a]
			inv(16)(p13.3q13)‡

See Appendix for explanation of locus symbols. * Including regions with only 1–3 reports of viable deletions. † Breakpoints not at established 11p15.4–.5 loci. ‡ Personal observation. § J Beck, personal communication. ‖ Cited in ref 87.

quency of rearrangements in mendelian disorders, but also for selection of strategies for their detection.

DISORDERS MAPPING TO REGIONS WHERE DELETIONS ARE VIABLE

Retinoblastoma, Wilms's tumour, and aniridia

The early detection of cases with deletion of a D group (No 13) chromosome in association with retinoblastoma (RB1)[38–40] led to extensive cytogenetic screening of large series of patients.[41–44] Consequently visible deletions have been found in 2 to 4% of all patients with RB1 when examined by metaphase technique, and in 4 to 8% of patients when examined by high resolution techniques. Reciprocal translocations have been detected in approximately 1% of patients in several independent surveys using both metaphase and prometaphase resolution, corresponding to 10% of the detected rearrangements. Thus, between 5 and 10% of all cases with RB1 have a visible chromosome mutation.

Larger systematic cytogenetic studies have not been reported in association with Wilms's tumour (WT1)/aniridia, so a direct comparison with the individual traits included in the Wilms's tumour/aniridia/genitourinary malformation/mental retardation (WAGR) complex cannot be made. However, in three large series of Wilms's tumour patients, altogether comprising 1335 cases,[45–47] aniridia was observed in 23 cases (1·7%). Furthermore, 1/3 of aniridia cases are sporadic and, of these, 1/3 develop Wilms's tumour.[48] A visible deletion of 11p13 was seen in all 18 cases with combined WT1/aniridia in three high resolution cytogenetic surveys,[47 49 50] supporting the fact that most subjects with this combination have a visible deletion. All evidence supports a single map position for aniridia at 11p13.[51] If so, 1/3 × 1/3 (10%) of independent cases with aniridia may have a visible deletion. Since both traits are easily recognised, this is in line with the large number of cases with the WAGR complex and deletions of 11p13 that have been reported.[52] As expected for contiguous gene syndromes, visible deletions and more complex rearrangements within 11p13 may not affect both loci.[50 53 54] The limited distance between WT1 and the candidate aniridia loci (700 to 1000 kb)[18 55] explains why a few persons with Wilms's tumour and aniridia have deletions below the limit of microscopic resolution.[55 56] Balanced chromosome rearrangements involving 11p13 have not been reported in association with Wilms's tumour, but one translocation with a breakpoint within the region has been seen in association with Potter syndrome,[57] and three reciprocal translocations have been reported in familial aniridia.[58–60] Taken together, the data are compatible with a frequency of chromosome rearrangements in all independent cases with WT1, aniridia, and WT1/aniridia in the same

range as observed in RB1 (2 to 10%), with deletions being by far the most frequent type of mutation.

Disorders associated with imprinting: Prader-Willi and Angelman syndromes

Repeated observations of rearrangements involving chromosome 15 in patients with Prader-Willi syndrome (PWCR) led to numerous systematic studies.[61–63] As a result, 60% of patients have been found to carry detectable chromosome 15 rearrangements, mostly deletions within 15q11–13 (table 1). The cytogenetic spectrum of 300 PWCR subjects with a chromosome 15 abnormality included 182 interstitial deletions, 34 unbalanced reciprocal translocations, 14 Robertsonian translocations, 16 small marker chromosomes, and four duplications,[61–63] plus six balanced translocations and one pericentric inversion.[61] The inversion was inherited from an unaffected father.[64] Assuming that 60% of PWCR cases have a cytogenetic defect, the frequency of apparently balanced rearrangements thus appears to be close to that of RB1 ($7 * 60/300 = 1{\cdot}4\%$). However, it should be emphasised that balanced rearrangements were not reported among 358 PWCR patients studied in larger chromosome surveys in the period 1981 to 1991.[61–63]

Cytogenetic deletion of 15q11–13 is also observed in 50 to 60% of subjects with Angelman syndrome (ANCR).[65–68] Among the fewer than 100 cases with ANCR that have been studied so far, one apparently balanced rearrangement has been reported, a maternally inherited inversion with a breakpoint within 15q13,[68] which was associated with a de novo submicroscopic deletion in the affected child.[69]

The frequency of visible deletions in RB1, PWCR, and ANCR thus varies considerably ($\sim$5 to 60%), whereas the frequency of apparently balanced cytogenetic rearrangements may be within the same order of magnitude ($\sim$1%).

X linked disorders

On the X chromosome, the male deletion viable regions involve Xp22.3, Xp21, Xq21, and Xq25 (figure).[37 70–74] Owing to the excellent morbid anatomy of the X chromosome,[29] these deletions are associated with recognisable mendelian traits, either as single gene disorders[73] or as part of contiguous gene syndromes.[37 70–72] In a survey of five males with DMD and additional clinical signs suggesting a contiguous gene disorder, visible deletions were detected in all five cases.[71] Bivariate flow karyotyping of 10 visible deletions within Xp21 associated with contiguous gene syndromes has provided a size estimate of these deletions in the range 4 to 14 Mb.[72]

The frequency of visible deletions in patients with single gene disorders mapping to Xp21 appears to be lower than observed in many autosomal disorders. In a systematic survey of 165 males with Duchenne or Becker muscular dystrophy only, no chromosome rearrangements were observed.[75] This may be somewhat surprising since submicroscopic deletions are extremely common in DMD, and since intragenic deletions in the 2·4 Mb DMD locus might potentially reach the lower limit of microscopic resolution.

Disease associated deletions involving the distal part of Xp22.3 are seen in both males and females, in males associated with recessive traits and in females with dominant traits.[70] Most other X chromosome deletions are preferentially inactivated in female carriers, either without phenotypic effects or associated with Turner symptoms, including gonadal dysgenesis or secondary amenorrhoea/premature menopause.[76] However, deletion of the region Xq27 may result in preferential activity of the deleted X chromosome,[77] and it has been suggested that this might be because of deletion of a locus which is involved in the normal X inactivation process.[78] If so, visible or submicroscopic deletions of Xq27 should be considered, along with X;autosome translocations, in females affected with disorders mapping to this region.

DISORDERS MAPPING TO REGIONS WHERE DELETIONS ARE NON-VIABLE

In contrast to deletions, breakpoints associated with constitutional autosome translocations detected in an unbiased way in large series of prenatal diagnoses[79] (figure), as well as in reported X;autosome translocations,[80 81] are distributed all over the genome. Hence, the presence of disease specific translocations would not be expected to be influenced by the chromosomal localisation of a disorder to the same extent as deletions. One modification of this is that the G-C rich chromosomal reverse (R) bands contain many more genes than the A-T rich G bands.[82 83] Therefore, disease specific breakpoints in translocations and inversions should predominantly be located in R bands, which is indeed the case (figure).

If RB1 is the prototype of a clearly recognised disease localised within a chromosomal region where gross deletion is compatible with fetal survival, Rubinstein-Taybi syndrome (RSTS), von Recklinghausen neurofibromatosis (NF1), and, to some extent, campomelic dysplasia (CMPD1) exemplify disorders mapping to regions where deletions do not or only rarely occur.

Rubinstein-Taybi syndrome, von Recklinghausen neurofibromatosis, and campomelic dysplasia

A locus for RSTS has been assigned to 16p13.3 after the identification of several independent chromosome rearrangements with breakpoints within this region.[84–87] Apart from small distal deletions associated with the haemoglobin H/mental retardation syndrome,[88] viable visible deletions of 16p13 have not been described at all.[27 85 87] This, together with the detection of submicroscopic deletions in 25% of RSTS subjects with normal karyotypes,[87] indicates that it is not deletions as such that do

not occur or that are not compatible with the RSTS phenotype, but rather the size of the deletions.

Both RB1 and WT1 are tumour suppressor loci.[89] However, it is unlikely that this feature in itself is associated with the high frequency of visible deletions seen in these disorders. Neurofibromatosis type 1 (NF1) also involves a tumour suppressor gene that maps to 17q11.2.[6] The largest deletion which has so far been described in a patient with NF1 was 380 kb in size,[90] well below the limit of microscopic resolution. This is in line with the general absence of reported constitutive deletions of this part of chromosome 17 (figure).[27] In the only published case with a visible deletion of the proximal part of 17q, the deleted segment was still present in most of the cells as a small ring chromosome.[91] In contrast, and by analogy with the findings in RSTS, reciprocal translocations have been described in NF1 (table 2).[92 93]

In campomelic dysplasia (CMPD1), chromosome analysis has been performed in a number of cases because of the frequent association with 46,XY sex reversal (SRA1).[94] Four de novo reciprocal translocations and one inversion, all involving 17q24–25, provide compelling evidence for the localisation of both CMPD1 and SRA1 to this region.[95–97] Only a few viable deletions involving the distal part of 17q have been reported.[98–100] Thus, CMPD1 may illustrate a disorder mapping to a region where viable deletions do occur, but only rarely. Although CMPD1/SRA1 has been suggested to be a contiguous gene syndrome,[95 101] visible deletions have not been reported in patients with CMPD1/SRA1. Thus, the observed pattern of chromosome rearrangements in CMPD1 resembles the pattern in disorders mapping to regions where deletions do not occur at all.

Disorders associated with imprinting: Beckwith-Wiedemann syndrome

Genetic imprinting of one or more loci within 11p15 has been implicated in the aetiology of Beckwith-Wiedemann syndrome.[102 103] As in Prader-Willi syndrome,[61 104] several different types of chromosome rearrangements have been encountered in BWS, including balanced rearrangements with breakpoints in the critical region of 11p15, exclusively of maternal origin, and duplications of the distal part of 11p15, exclusively of paternal origin (table 2). It has been suggested that the duplications lead to excess expression of a paternally imprinted growth promoting gene within the region, such as insulin growth factor 2 (IGF2), whereas the balanced translocations might affect a maternally imprinted regulator within the region.[103] Viable deletions involving the distal part of 11p15 have not been described,[27] so it is not likely that such deletions will be seen in association with BWS either.

X linked disorders

Menkes disease illustrates an X linked disorder which maps to an R band region (Xq13.3) where visible deletions have not been described in males.[105 106] In a continuing cytogenetic survey of more than 200 unrelated males with Menkes disease, not a single case with a visible deletion has been detected.[107]

Although the proven X linked contiguous gene syndromes map to those regions where cytogenetic deletions are viable, X linked contiguous gene syndromes located within most R band regions would be expected to be more numerous, considering the high gene density of R bands. However, these disorders will probably be associated with either submicroscopic rearrangements[108] or with 'balanced' rearrangements which will lead to limited loss of material. The same argument applies to autosomal contiguous gene syndromes mapping to deletion non-viable regions.

So far, few mendelian disorders have been associated with visible duplications.[103 109] In general, duplications are better tolerated than deletions,[27] so a smaller part of the genome will be duplication non-viable. However, it is reasonable to assume that for disorders associated with duplication of genetic material, the chromosomal localisation may also influence the occurrence of visible chromosome mutations.

The effect of the parental origin of de novo chromosome rearrangements

De novo chromosome rearrangements are predominantly of paternal origin, including all X;autosome translocations examined so far.[95 110–116] This skewed parental origin has several implications for the detection of structural rearrangements in mendelian disorders.

DE NOVO REARRANGEMENTS OF THE X CHROMOSOME

As most chromosome rearrangements are paternal in origin, those involving the X must occur predominantly in females, where the phenotypic effect will be influenced by the X inactivation pattern. In balanced X;autosome translocations, where the translocation X is as a rule the active one,[80 81] truncation of a disease gene will lead to affected status in the female carrier. This mechanism is a main contributor to the disproportionately large number of X linked disorders where structural rearrangements have been described (figure). Since affected females with normal chromosomes are less likely to be reported, the actual frequency of X;autosome translocations in affected females is unknown. The best estimate may come from Menkes disease (MNK), where diagnosis, including that of females, has been centralised to a few centres in the world. So far, two of six known MNK females are translocation carriers (J Beck, personal communication).[107 117]

Males will only inherit an X;autosome translocation if the translocation does not lead to gonadal dysgenesis, a frequent finding in females with breakpoints on the X chromosome.[76] In addition, an associated mendelian disorder in the mother will have to be suffi-

ciently mild to allow reproduction. As a consequence, X;autosome translocations are in general rare in males.[80 118] This, together with the presumed male non-viability of deletions involving the major part of the X chromosome (figure), led to the suggestion that intrachromosomal rearrangements, such as inversions and shifts, will be likely types of cytogenetic rearrangements in males affected with most X linked disorders.[107] These rearrangements are probably very rare.[119–121]

DISORDERS WHERE GENOMIC IMPRINTING IS INVOLVED

As discussed previously, deletions involving almost the same region of 15q11–13 are frequently observed in both PWCR and ANCR. However, the deletion is always of paternal origin in PWCR[61–63] and always of maternal origin in ANCR.[122] Although the proportion of affected subjects carrying a cytogenetically visible deletion is the same in the two disorders, two significant aetiological factors support a higher frequency of PWCR than ANCR: (1) the large excess of maternal non-disjunction[123] that may predispose to subsequent uniparental maternal disomy, as observed in PWCR,[124 125] and (2) the presumed higher frequency of de novo rearrangements (deletions) of paternal origin which will also lead to PWCR.

In Beckwith-Wiedemann syndrome, all balanced rearrangements involving the distal part of 11p15 have been found to be inherited from the mother, similar to a preponderance of maternal transmission of BWS in non-cytogenetic familial cases.[103 126] Together with the predominantly paternal origin of de novo rearrangements, this implies that few if any de novo balanced rearrangements will be observed in subjects affected with BWS. In contrast, the mother may frequently carry the balanced rearrangement as a de novo rearrangement of paternal origin, or may have inherited the rearrangement from her father.

A similar sex dependent transmission pattern might be possible in balanced rearrangements associated with ANCR[69] and PWCR,[61 64] where the phenotypic effect of truncation or deletion[69] will be influenced by the parental origin of the inherited rearrangement.[68] Thus, apparently balanced rearrangements in PWCR should be of paternal origin,[64] and of maternal origin in ANCR.[69]

It has now become an almost routine procedure to search for the parental origin of chromosome rearrangements. Owing to the excess of de novo rearrangements of paternal origin, demonstration of a maternal origin of de novo rearrangements in a specific disorder will be much more significant with respect to a possible involvement of genomic imprinting[122] than demonstration of a paternal origin.[95]

Mutational aspects with relevance for positional cloning

ARE BREAKPOINTS IN BALANCED REARRANGEMENTS LOCUS SPECIFIC?

Although the majority of reciprocal translocations and inversions included in tables 1 and 2 are balanced at the cytogenetic level, a few of these have been shown to be associated with large submicroscopic deletions.[127 128] If this were a general feature, the assumption that these rearrangements involve single breaks within the target locus would be erroneous.[93] However, of 23 apparently balanced rearrangements studied at the gene level,[129–138] 22 had breakpoints within the candidate gene locus (table 3). The assumed locus specificity of breakpoints in cytogenetically balanced rearrangements in mendelian disorders therefore seems justified, even though these rearrangements may not be truly conserved at the sequence level, since small deletions from a few bp to <30 kb have been noted (table 3).

LOCALISATION OF BREAKPOINTS OUTSIDE THE SPECIFIC TARGET

Six unrelated reciprocal translocations have been reported in retinoblastoma patients,[41] along with 14 specific reciprocal and eight insertional translocations. The odds therefore seem to favour a rearrangement as being disease specific. However, they also illustrate that the coincidental occurrence of a rearrangement is not uncommon. Further studies of the family, linkage studies in other families, search for similar published reports, and comparison with the clinical features associated with deletions or duplications of the regions involved are needed when considering the significance of a detected rearrangement.

Even if a structural chromosome mutation turns out to be the aetiological factor, some mutational mechanisms have been documented or suggested which may limit the utility of both balanced and unbalanced rearrangements for positional cloning, or at least provide

Table 3 Molecular details of assumed locus specific rearrangements.

Disorder (locus symbol)	No of studied rearrangements	No which truncate the specific locus	No with sequenced/ estimated deletion	Size of deletion
DMD	11	11[129–132]	2	71/72 bp[129] 5 kb[132]
GCPS	3	2[166]		
MNK	2	2[138 251 252]		
NF1	1	1[135]		
RB1	4	4[133 134]	1	<30 kb[134]
TCD	1	1[136]		
WS1	1	1[137]		
Total	23	22		

conflicting data as to the disease or locus specificity.

Spreading of X inactivation in X;autosome translocations

Although the majority of X;autosome translocations associated with mendelian disorders have involved the X linked locus, it would be logical to assume that the autosomal breakpoint would occasionally represent the target. Most of the documented cases have been X;13 translocations associated with RB1.[41 139] At the cytogenetic level, 13q14 harbouring the RB1 locus seemed to be intact in all cases. The suggested mechanism for the development of RB1 in these cases is spreading of X inactivation into the autosomal segment including the RB1 locus.[139] Inactivation of a putative locus at 9q32–34 by spreading of X inactivation has also been suggested in two X;autosome translocation carrying girls with incontinentia pigmenti or hypomelanosis of Ito.[140]

The paradox of incontinentia pigmenti (IP1 and IP2)

At least seven, possibly eight,[9] X chromosome rearrangements have been detected in sporadic cases of IP, with most of the breakpoints within Xp11.[141–147] IP is considered an X linked dominant disorder, which is lethal in males, and which only occurs in females as a result of the functional mosaicism associated with random lyonisation. The paradoxes of IP are as follows. (1) The locus for familial IP has been assigned to Xq28 by linkage analysis and not to Xp11.[148 149] Therefore, two loci associated with IP (IP1 and IP2) have been invoked. (2) It has been suggested that two, maybe three, of the translocation carriers[143 145] did not have IP but hypomelanosis of Ito (HI).[140 150] HI has been considered the 'negative' of IP because the abnormal hypopigmented skin areas are distributed in the same pattern. The disorder may be a clinical manifestation of mosaicism or chimerism, as evidenced by the frequent association with chromosomal mosaicism involving a variety of different chromosomes.[150 151] (3) Several different X chromosome breakpoints have been detected in the chromosomal rearrangements associated with IP.[152–154] The distance between two distinct regions of breakpoints within Xp11, one close to the centromere and one more distal, is at least 2·5 Mb,[154] suggesting that if IP1 exists, the locus must be extremely large, or several loci within Xp11 may be involved. (4) Of two of the translocations stated to be associated with HI, one maps to the distal region and one to the proximal region in Xp11.[154]

Considering the similar distribution of skin defects in IP and HI, the defect in these sporadic cases with IP may also involve somatic mosaicism, perhaps associated with X inactivation. One of the rearrangements involved a r(X),[141] so dynamic mosaicism associated with ring chromosome instability might even be involved,[155] in which case the gene(s) responsible for the pigmentary abnormalities might be situated anywhere on the X chromosome (for example, IP2 in Xq28). One implication of this would be that positional cloning of a putative IP1 locus defined by X chromosome breakpoints[154] may be impossible.

Unmasking of mutations by rearrangement induced non-random X inactivation

If the normal X chromosome contains a mutated locus, non-random X inactivation of a structurally abnormal X chromosome may incidentally lead to clinically affected status of a female.[156] The erroneous conclusion that the disease locus is regionally defined by the breakpoints of the rearrangement may be avoided by careful X inactivation studies. The possibility exists that this mechanism may be involved in IP1. It is uncertain whether a similar mechanism might be involved in two X;autosome translocations with different breakpoints on Xp in Rett syndrome,[157 158] a disorder in which X linkage has been suggested by almost exclusive involvement of girls, but where linkage analysis seems to have excluded the X chromosome.[159]

Localisation of breakpoints close to but outside the open reading frame

The locus for Greig cephalopolysyndactyly (GCPS) has been pinpointed to 7p13 by three balanced familial translocations,[160–162] by deletions,[163 164] and by linkage studies.[165] By the candidate gene approach,[7] two of the three familial translocations were found to interrupt a zinc finger gene GLI3 located within 7p13.[166] However, the breakpoint in the third translocation occurred about 10 kb downstream of the 3′ end of GLI3. It was speculated that as a result a *cis* acting element was brought into the region of GLI3, thereby deregulating its expression.[166]

Dynamic mosaicism associated with ring chromosomes

Carriers of ring chromosomes harbouring tumour suppressor genes may be at increased risk of developing chromosome specific types of tumours, for example, r(13) carriers may develop RB1, r(11) carriers WT1, r(22) carriers meningioma, etc.[155] Conversely, the development of a specific type of tumour in a ring carrier may suggest that a tumour suppressor locus is located somewhere on that chromosome. Apart from the primary deletion associated with the formation of the ring, ring chromosomes are predisposed to secondary somatic rearrangements initiated by sister chromatid exchanges. The result may be fragmentation, gain or loss of ring material, including complete monosomy (dynamic mosaicism). A comparison between the localisation of the primary breakpoints and the likely tumour suppressor loci involved suggests that the secondary instability may be the most important factor predisposing to the development of tumours.[155] Thus, unlike conventional constitutional deletions which can be used for the

generation of disease related deletion maps, correlations between the primary ring associated deletions and phenotypic features should be regarded with caution.

Dynamic mosaicism may not be limited to the development of tumours, but should also be considered as a possible mechanism in the development of other disorders in ring carriers. One possible association is Russell–Silver syndrome which shares many clinical features with ring chromosome 15 deficiencies.[167]

Conclusions

The present review has primarily been concerned with those rearrangements which can be expected to be encountered in a majority of mendelian disorders. Thus, the fragile site at Xq27 associated with the most common form of X linked mental retardation has not been discussed since it is so far the only fragile site known to be associated with a specific clinical entity.

Although deletions occur less frequently than reciprocal translocations in newborn screening series,[33] any deletion of visible size will have a big chance of involving part or all of a gene. This may explain why viable deletions are the most frequent type of cytogenetic mutation in mendelian disorders. In contrast, a single breakpoint or a submicroscopic deletion associated with a translocation or inversion has to be more precisely located in order to involve a specific locus.

The majority of visible deletions associated with mendelian disorders has been observed in sporadic cases (tables 1 and 2). A few exceptions have been reported, which may be explained by the presence of mosaicism in a parental carrier, or a less severe phenotype associated with small deletions within certain regions, such as 13q14 associated with RB1.[41] In most other situations, the assumption that chromosomal deletions are reproductive lethal mutations is probably true. However, familial occurrence of deletions associated with mendelian disorders can be expected in two conditions: deletions involving the male deletion viable regions of the X chromosome, and familial translocations, especially insertional translocations.[41 54 168–172]

Apart from insertional translocations, other rare types of familial and sporadic rearrangements have been identified in association with mendelian disorders, in part during chromosomal surveys.[91 106] As mentioned previously, intrachromosomal rearrangements, including shifts, may be the expected type of chromosome mutation in males affected with the majority of X linked diseases.[107] Whether this apparent accumulation of otherwise rare types of rearrangement may reflect ascertainments which are different from those usually encountered in cytogenetics (prenatal diagnosis, MCA/MR, spontaneous abortions, etc) is at present unknown.

Without valid data derived from systematic cytogenetic surveys in the majority of disorders, the best estimate of a basic frequency of chromosome rearrangements in an autosomal dominant disorder is approximately 1%, corresponding to the frequency of balanced translocations and inversions observed in RB1 (and maybe in PWCR and ANCR). If, in addition, visible deletions within the specific chromosome region are viable, this figure will be considerably higher.

The data favour that cytogenetic rearrangements will be present in a small, but not insignificant, fraction of subjects affected with many mapped and unmapped mendelian disorders. The detection of a chromosome mutation will have obvious counselling implications in the individual family. Considering the impact even a single specific rearrangement may have for gene mapping and cloning, a more systematic effort to detect these rearrangements should be pursued. In terms of value for rapid molecular isolation of the locus of interest, rearrangements involving locus specific breaks (for example, balanced translocations and inversions) will in general be the most valuable ones. Although the presence of additional congenital anomalies, other unexpected diseases, spontaneous abortions, stillbirths, etc, may suggest the involvement of a chromosome mutation in a patient or within a family, subjects with balanced rearrangements may not suffer from additional disorders.[107] Furthermore, translocations and inversions may be both familial and de novo mutations (tables 1 and 2). Therefore, some of the most valuable mutations in terms of positional cloning may only be detected by systematic analysis.

If a reciprocal translocation is detected in a disorder that has not been mapped previously, the odds will favour a breakpoint within an R band being the specific one. In some cases this may ease subsequent attempts to confirm the specificity of new translocations, for example, by linkage mapping. Furthermore, for large scale screening programmes, high resolution chromosome analysis may be too cumbersome and time consuming. Screening strategies can be devised which in part will alleviate this. In disorders with a known chromosomal localisation, complete karyotyping by high resolution technique may not be needed. In disorders mapping to regions where deletions are unlikely to be viable, normal good quality metaphase technique may be sufficient to detect the single break rearrangements that can be expected. In addition, the deletion map shown in the figure may provide a basis for tentative exclusion mapping of mainly autosomal dominant disorders, where repeated chromosome analysis has failed to identify rearrangements. Such disorders might be expected to map within the deletion non-viable or less viable part of the genome. This was the case with two of the most recently mapped disorders, RSTS[85 87] and CMPD1.[95]

Linkage mapping will be greatly eased by the rapidly increasing numbers of highly polymorphic microsatellites which can be analysed by the PCR technique.[173] In this context a continuous registration and clinical follow up of subjects with known chromosome re-

arrangements will become increasingly important. Whenever a disease has been mapped to a specific chromosome region, rapid reinvestigation of subjects carrying chromosome rearrangements within that region for key clinical features may provide essential mapping and clinical data. This approach was used successfully to detect choroideraemia[174] in a patient with a previously reported Xq21 deletion,[175] and to show reduced nerve conductance velocity in a patient with a large visible duplication encompassing the CMT1A locus on 17p.[109]

The rapid construction of complete YAC and cosmid contigs[176 177] will greatly facilitate future mapping and isolation of specific disease breakpoints/genes, for example, in combination with in situ hybridisation techniques. The detection of rearrangements associated with mendelian diseases will therefore remain an important challenge for the clinical cytogeneticist. Many cytogenetic laboratories may be discouraged from systematic studies by the rarity of mendelian disorders and by the expectation of a relatively low frequency of associated cytogenetic rearrangements. As has been shown so convincingly in other fields of human genome mapping, concerted action would be the logical way to ensure a systematic detection of these highly valuable mutations in man.

This study was supported by the Danish Cancer Society (89-059, 90-021), the Norwegian Cancer Society, the Danish Medical Research Council (12-9292, 12-9744, 12-7414, 5.17-.4.2.53), The Foundation of 1870, and the Danish Biotechnology Research and Development Programme 1991–95 (5.18.03).

1 Greenstein RM, Reardon MP, Chan TS. An X-autosome translocation in a girl with Duchenne muscular dystrophy (DMD): evidence for DMD gene location. *Pediatr Res* 1977;**11**:457.
2 Verellen C, Markovic V, DeMeyer R, *et al.* Expression of an X-linked recessive disease in a female due to non-random inactivation of the X chromosome. *Am J Hum Genet* 1978;**30**:97A.
3 Canki CT, Dutrillaux B, Tivadar I. Dystrophie musculaire de Duchenne chez une petite fille porteuse d'une translocation t(X;3)(p21;q13) de novo. *Ann Genet (Paris)* 1979;**22**:35–9.
4 Lindenbaum RH, Clarke G, Patel C, *et al.* Muscular dystrophy in an X;1 translocation female suggests that Duchenne locus is on X chromosome short arm. *J Med Genet* 1979;**16**:389–92.
5 Jacobs PA, Hunt PA, Mayer M, Bart RD. Duchenne muscular dystrophy (DMD) in a female with an X/autosome translocation: further evidence that the DMD locus is at Xp21. *Am J Hum Genet* 1981;**33**:513–18.
6 Frézal J, Schinzel A. Report of the committee on clinical disorders and chromosomal deletion syndromes (HGM11). *Cytogenet Cell Genet* 1991;**58**:986–1052.
7 Collins FS. Positional cloning: let's not call it reverse anymore. *Nature Genet* 1992;**1**:3–6.
8 Edwards JH. Chromosomal abnormalities in mendelian disorders. *Lancet* 1982;**i**:322–3.
9 McKusick VA. *Mendelian inheritance in man. Catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes.* 10th ed. Baltimore: Johns Hopkins University Press, 1992.
10 Stratton R, Dobyns WB, Airhart SD, Ledbetter DH. New chromosomal syndrome: Miller-Dieker syndrome and monosomy 17p13. *Hum Genet* 1984;**67**:193–200.
11 Greenberg F, Stratton RF, Lockhart LH, *et al.* Familial Miller-Dieker syndrome associated with pericentric inversion of chromosome 17. *Am J Med Genet* 1986;**23**:853–9.
12 Kuwano A, Ledbetter SA, Dobyns WB, Emanuel BS, Ledbetter DH. Detection of deletions and cryptic translocations in Miller-Dieker syndrome by in situ hybridization. *Am J Hum Genet* 1991;**49**:707–14.
13 Schmickel RD. Contiguous gene syndromes: a component of recognizable syndromes. *J Pediatr* 1986;**109**:231–41.
14 Emanuel BS. Molecular cytogenetics: toward dissection of the contiguous gene syndromes. *Am J Hum Genet* 1988;**43**:575–8.
15 Rose EA, Glaser T, Jones C, *et al.* Complete physical map of the WAGR region of 11p13 localizes a candidate Wilms' tumor gene. *Cell* 1990;**60**:405–8.
16 Call KM, Glaser T, Ito CY, *et al.* Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus. *Cell* 1990;**60**:509–20.
17 Gessler M, Poustka A, Cavenee W, *et al.* Homozygous deletion in Wilms' tumours of a zinc-finger gene identified by chromosome jumping. *Nature* 1990;**343**:774–8.
18 Gessler M, Simola KOJ, Bruns GAP. Cloning of breakpoints of a chromosome translocation identifies the AN2 locus. *Science* 1989;**244**:1575–8.
19 Ton CCT, Hirvonen H, Miwa H, *et al.* Positional cloning and characterization of a paired box- and homeobox-containing gene from the aniridia region. *Cell* 1991;**67**:1059–74.
20 Haber DA, Buckler AJ, Glaser T, *et al.* An internal deletion within an 11p13 zinc finger gene contributes to the development of Wilms' tumor. *Cell* 1990;**61**:1257–69.
21 Pelletier J, Bruening W, Li FP, *et al.* WT1 mutations contribute to abnormal genital system development and hereditary Wilms' tumour. *Nature* 1991;**353**:431–4.
22 Pelletier J, Bruening W, Kashtan CE, *et al.* Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. *Cell* 1991;**67**:437–47.
23 Bruening W, Bardeesy N, Silverman BL, *et al.* Germline intronic and exonic mutations in the Wilms' tumour gene (WT1) affecting urogenital development. *Nature Genet* 1992;**1**:144–8.
24 Jordan T, Hanson I, Zaletayev D, *et al.* The human PAX6 gene is mutated in two patients with aniridia. *Nature Genet* 1992;**1**:328–32.
25 Ledbetter SA, Kuwano A, Dobyns WB, Ledbetter DH. Microdeletions of chromosome 17p13 as a cause of isolated lissencephaly. *Am J Hum Genet* 1992;**50**:182–9.
26 Dobyns WB, Elias ER, Newlin AC, Pagon RA, Ledbetter DH. Causal heterogeneity in isolated lissencephaly. *Neurology* 1992;**42**:1375–88.
27 Schinzel A. *Catalogue of unbalanced chromosomal aberrations in man.* Berlin: Walter deGruyter, 1984.
28 Smith ACM, McGavran L, Robinson J, *et al.* Interstitial deletion of (17)(p11.2p11.2) in nine patients. *Am J Med Genet* 1986;**24**:393–414.
29 McKusick VA, Amberger JS. The morbid anatomy of the human genome: chromosomal location of mutations causing disease. *J Med Genet* 1993;**30**:1–26.
30 Naritomi K, Hyakuna N, Suzuki Y, Orii T, Hirayama K. Zellweger syndrome and a microdeletion of the proximal long arm of chromosome 7. *Hum Genet* 1988;**80**:201–2.
31 Naritomi K, Izumikawa Y, Ohshiro S, *et al.* Gene assignment of Zellweger syndrome to 7q11.23: report of the second case associated with a pericentric inversion of chromosome 7. *Hum Genet* 1989;**84**:79–80.
32 Bühler EM. Unmasking of heterozygosity by inherited balanced translocations. Implications for prenatal diagnosis and gene mapping. *Ann Genet (Paris)* 1983;**26**:133–7.
33 Hook EB, Hamerton JL. The frequency of chromosome abnormalities detected in consecutive newborn studies—differences between studies—results by sex and by severity of phenotypic involvement. In: Hook EB, Porter IH, eds. *Population cytogenetics.* New York: Academic Press, 1977: 81–97.
34 Searle AG. Chromosomal variants. In: Lyon MF, Searle AG, eds. *Genetic variants and strains of the laboratory mouse.* 2nd ed. Oxford: Oxford University Press, 1989:582–616.
35 Pentao L, Lewis RA, Ledbetter DH, Patel PI, Lupski JR. Maternal uniparental isodisomy of chromosome 14: association with autosomal recessive rod monochromacy. *Am J Hum Genet* 1992;**50**:690–9.
36 Fannemel M, Riise R, Lofterød B, Tommerup N. High-resolution chromosome analysis in autosomal recessive disorders. Laurence-Moon-Bardet-Biedl syndrome. *Clin Genet* 1993;**43**:111–12.
37 Cremers FPM, van de Pol TJR, Wierenga B, *et al.* Molecular analysis of male-viable deletions and duplications allows ordering of 52 DNA probes on proximal Xq. *Am J Hum Genet* 1988;**43**:452–61.
38 Lele KP, Penrose LS, Stallard HB. Chromosome deletion in a case of retinoblastoma. *Ann Hum Genet* 1963;**27**:171–4.
39 Wilson MG, Melnyk J, Towner JWJ. Retinoblastoma and deletion D(14) syndrome. *J Med Genet* 1969;**6**:322–7.
40 Taylor AI. Dq-, Dr and retinoblastoma. *Humangenetik* 1970;**10**:209–17.
41 Munier F, Pescia G, Jotterand-Bellomo M, *et al.* Constitutional karyotype in retinoblastoma. Case report and review of literature. *Ophthalmic Paediatr Genet* 1989;**10**:129–50.
42 Cowell JK, Hungerford J, Rutland P, Jay M. Genetic and cytogenetic analysis of patients showing reduced esterase-D levels and mental retardation from a survey of 500 individuals with retinoblastoma. *Ophthalmic Paediatr Genet* 1989;**10**:117–27.
43 Bunin GR, Emanuel BS, Meadows AT, *et al.* Frequency of 13q abnormalities among 203 patients with retinoblastoma. *J Natl Cancer Inst* 1989;**81**:370–4.
44 Lemieux N, Richer CL. Chromosome evolution and high-resolution analysis of leucocytes, bone marrow, and tumor cells of retinoblastoma patients. *Am J Med Genet* 1990;**36**:456–62.
45 Miller RW, Fraumeni JF Jr, Manning MD. Association of

Wilms's tumor with aniridia, hemihypertrophy, and other congenital malformations. *N Engl J Med* 1964;**270**:922–7.
46 Pendergrass TW. Congenital anomalies in children with Wilms' tumor. A new survey. *Cancer* 1976;**37**:403–9.
47 Shannon RS, Mann JR, Harper E, *et al.* Wilms's tumour and aniridia: clinical and cytogenetic features. *Arch Dis Child* 1982;**57**:685–90.
48 Fraumeni JF Jr, Glass AG. Wilms's tumor and congenital aniridia. *JAMA* 1968;**206**:825–8.
49 Nakagome Y, Ise T, Sakurai M, *et al.* High-resolution studies in patients with aniridia–Wilms tumor association, Wilms tumor or related congenital abnormalities. *Hum Genet* 1984;**67**:245–8.
50 Hotta Y, Fujiki K, Ishida N, *et al.* High resolution G-banding analysis in aniridia. *Ophthalmic Paediatr Genet* 1987;**8**:145–50.
51 Lyons LA, Martha A, Mintz-Hittner HA, *et al.* Resolution of the two loci for autosomal dominant aniridia, AN1 and AN2, to a single locus on chromosome 11p13. *Genomics* 1992;**13**:925–30.
52 Turleau C, de Grouchy J, Tournade MF, Gagnadoux MF, Junien C. Del 11p/aniridia complex: report of three patients and review of 37 observations from the literature. *Clin Genet* 1984;**26**:356–62.
53 Turleau C, de Grouchy J, Nihoul-Fékété C, *et al.* Del11p13/nephroblastoma without aniridia. *Hum Genet* 1984;**67**:455–6.
54 Niikawa N, Fukushima Y, Taniguchi N, Iizuka S, Kajii T. Chromosome abnormalities involving 11p13 and low erythrocyte catalase activity. *Hum Genet* 1982;**60**:373–5.
55 Fantes JA, Bickmore WA, Fletcher JM, Ballesta F, Hanson M, van Heyningen V. Submicroscopic deletions at the WAGR locus, revealed by nonradioactive in situ hybridization. *Am J Hum Genet* 1992;**51**:1286–94.
56 Riccardi VM, Hittner HM, Strong LC, *et al.* Wilms tumor with aniridia/iris dysplasia and apparently normal chromosomes. *J Pediatr* 1982;**100**:574–7.
57 Porteous DJ, Bickmore W, Christie S, *et al.* HRAS1-selected chromosome transfer generates markers that colocalize aniridia- and genitourinary dysplasia-associated translocation breakpoints and the Wilms' tumor gene within 11p13. *Proc Natl Acad Sci USA* 1987;**84**:5355–9.
58 Moore JW, Hyman S, Antonarakis SE, Mules EH, Thomas GH. Familial isolated aniridia associated with a translocation involving chromosome 11 and 22 [t(11;22)(p13;q12.2)]. *Hum Genet* 1986;**72**:297–302.
59 Pettenati MJ, Weaver RG, Burton BK. Translocation t(5;11)(q13.1;p13) associated with familial isolated aniridia. *Am J Med Genet* 1989;**34**:230–2.
60 Simola KOJ, Knuutila S, Kaitila I, Pirkola A, Pohja P. Familial aniridia and translocation t(4;11)(q22;p13) without Wilms' tumor. *Hum Genet* 1983;**63**:158–61.
61 Butler MG. Prader-Willi syndrome: current understanding of cause and diagnosis. *Am J Med Genet* 1990;**35**:319–32.
62 Robinson WP, Bottani A, Yagang X, *et al.* Molecular, cytogenetic, and clinical investigations of Prader-Willi syndrome patients. *Am J Hum Genet* 1991;**49**:1219–34.
63 Hamabe J, Fukushima Y, Harada N, *et al.* Molecular study of the Prader-Willi syndrome: deletion, RFLP, and phenotype analyses in 50 patients. *Am J Med Genet* 1991;**41**:54–63.
64 Winsor EJT, Welch JP. Prader-Willi syndrome associated with inversion of chromosome 15. *Clin Genet* 1983;**24**:456–61.
65 Fryns JP, Kleczkowska A, Decock P, Van den Berghe H. Angelman's syndrome and 15q11–13 deletions. *J Med Genet* 1989;**26**:538–40.
66 Hamabe J, Kuroki Y, Imaizumi K, *et al.* DNA deletion and its parental origin in Angelman syndrome patients. *Am J Med Genet* 1991;**41**:64–8.
67 Imaizumi K, Takada F, Kuroki Y, *et al.* Cytogenetic and molecular study of Angelman syndrome. *Am J Med Genet* 1990;**35**:314–18.
68 Pembrey M, Fennell SJ, Van den Berghe J, *et al.* The association of Angelman's syndrome with deletions within 15q11–13. *J Med Genet* 1989;**26**:73–7.
69 Webb T, Clayton-Smith J, Cheng XJ, *et al.* Angelman syndrome with a chromosomal inversion 15 inv(p11q13) accompanied by a deletion in 15q11q13. *J Med Genet* 1992;**29**:921–4.
70 Ballabio A, Andria G. Deletions and translocations involving the distal short arm of the human X chromosome. Review and hypotheses. *Hum Mol Genet* 1992;**1**:221–7.
71 Matsumoto T, Kondoh, Yoshimoto M, *et al.* Complex glycerol kinase deficiency: molecular-genetic, cytogenetic, and clinical studies of five Japanese patients. *Am J Med Genet* 1988;**31**:603–16.
72 McCabe ERB, Towbin JA, van den Engh G, Trask BJ. Xp21 contiguous gene syndromes: deletion quantitation with bivariate flow karyotyping allows mapping of patient breakpoints. *Am J Hum Genet* 1992;**51**:1277–85.
73 Wyandt HE, Grierson HL, Sanger WG, *et al.* Chromosome deletion of Xq25 in an individual with X-linked lymphoproliferative disease. *Am J Med Genet* 1989;**33**:426–30.
74 Yang HM, Lund T, Niebuhr E, *et al.* Exclusion mapping of 12 X-linked disease loci and 10 DNA probes from the long arm of the X-chromosome. *Clin Genet* 1990;**38**:94–104.
75 Thomas NST, Ray PN, Worton RG, Harper PS. Molecular deletion analysis in Duchenne muscular dystrophy. *J Med Genet* 1986;**23**:509–15.
76 Therman E, Susman B. The similarity of phenotypic effects caused by Xp and Xq deletions in the human female: a hypothesis. *Hum Genet* 1990;**85**:175–83.
77 Schmidt M, Certoma A, Du Sart D, *et al.* Unusual X chromosome inactivation in a mentally retarded girl with an interstitial deletion Xq27: implications for the fragile X syndrome. *Hum Genet* 1990;**84**:347–52.
78 Schmidt M. Do sequences in Xq27.3 play a role in X inactivation? *Am J Med Genet* 1992;**43**:487–91.
79 Daniel A, Hook EB, Wulf G. Collaborative USA data on prenatal diagnosis for parental carriers of chromosome rearrangements: risks of unbalanced progeny. In: *The cytogenetics of mammalian autosomal rearrangements*. New York: Alan R Liss, 1988:73–162.
80 Mattei MG, Mattei JF, Ayme S, Giraud F. X-autosome translocation: cytogenetic characteristics and their consequences. *Hum Genet* 1982;**61**:295–309.
81 Schmidt M, Du Sart D. Functional disomies of the X chromosome influence the cell selection and hence the X inactivation pattern in females with balanced X-autosome translocations: a review of 122 cases. *Am J Med Genet* 1992;**42**:161–9.
82 Korenberg JR, Rykowski MC. Human genome organization: Alu, Lines, and the molecular structure of metaphase chromosome bands. *Cell* 1988;**53**:391–400.
83 Holmquist GP. Chromosome bands, their chromatin flavors, and their functional features. *Am J Hum Genet* 1992;**51**:17–37.
84 Imaizumi K, Kuroki Y. Rubinstein-Taybi syndrome with de novo reciprocal translocation t(2;16)(p13.3;p13.3). *Am J Med Genet* 1991;**38**:636–9.
85 Tommerup N, van der Hagen CB, Heiberg A. Tentative assignment of a locus for Rubinstein-Taybi syndrome to 16p13.3 by a de novo reciprocal translocation, t(7;16)(q34;p13.3). *Am J Med Genet* 1992;**44**:237–41.
86 Lacombe D, Saura R, Taine L, Battin J. Confirmation of assignment of a locus for Rubinstein-Taybi syndrome to 16p13.3. *Am J Med Genet* 1992;**44**:126–8.
87 Breuning MH, Dauwerse HG, Fugazza G, *et al.* Rubinstein-Taybi syndrome caused by submicroscopic deletions within 16p13.3. *Am J Hum Genet* 1993;**52**:249–54.
88 Wilkie AO, Buckle VJ, Harris PC, *et al.* Clinical features and molecular analysis of the alpha thalassemia/mental retardation syndromes. I. Cases due to deletions involving chromosome band 16p13.3. *Am J Hum Genet* 1990;**46**:1112–26.
89 Weinberg RA. Tumor suppressor genes. *Science* 1991;**254**:1138–46.
90 Kayes LM, Riccardi VM, Burke W, Bennett RL, Stephens K. Large de novo deletion in a patient with sporadic neurofibromatosis 1, mental retardation, and dysmorphism. *J Med Genet* 1992;**29**:686–90.
91 Andersen LB, Tommerup N, Koch J. Formation of a mini-chromosome by excision of the proximal region of 17q in a patient with von Recklinghausen neurofibromatosis. *Cytogenet Cell Genet* 1990;**53**:206–10.
92 Schmidt MA, Michels VV, Deward W. Cases of neurofibromatosis with rearrangements of chromosome 17 involving band 17q11.2. *Am J Med Genet* 1987;**28**:771–7.
93 Ledbetter DH, Rich DC, O'Connell P, Leppert M, Carey JC. Precise localisation of NF1 to 17q11.2 by balanced translocation. *Am J Hum Genet* 1989;**44**:20–4.
94 Houston CS, Opitz JM, Spranger JW, *et al.* The campomelic syndrome: review, report of 17 cases, and follow-up on the currently 17-year-old boy first reported by Maroteaux et al in 1971. *Am J Med Genet* 1983;**15**:3–28.
95 Tommerup N, Schempp W, Meinecke P, *et al.* Assignment of an autosomal sex reversal locus (SRA1) and campomelic dysplasia (CMPD1) to 17q24.3–q25.1. *Nature Genet* 1993;**4**:170–4.
96 Maraia R, Saal HM, Wangsa D. A chromosome 17q de novo paracentric inversion in a patient with campomelic dysplasia; case report and etiologic hypothesis. *Clin Genet* 1991;**39**:401–8.
97 Young ID, Zuccollo JM, Maltby EL, Broderick NJ. Campomelic dysplasia associated with a de novo 2q;17q reciprocal translocation. *J Med Genet* 1992;**29**:251–2.
98 Bridge J, Sanger W, Mosher G, *et al.* Partial deletion of distal 17q. *Am J Med Genet* 1985;**21**:225–9.
99 Giannotti A, Alessandri A, Reale A, Digilio MC, Valorani MG. Partial deletion of the long arm of chromosome 17. Clinical case. *Minerva Pediatr* 1992;**44**:51–4.
100 Luke S, Bennett HS, Pitter JH, Verma RS. A new case of monosomy for 17q25-qter due to a maternal translocation [t(3;17)(p12;q24)]. *Ann Genet (Paris)* 1992;**35**:48–50.
101 Ebensperger C, Jäger RJ, Lattermann U, *et al.* No evidence of mutations in four candidate genes for male sex determination/differentiation in sex-reversed XY females with campomelic dysplasia. *Ann Genet (Paris)* 1991;**34**:233–8.
102 Henry I, Bonaïti-Pellié C, Junien C. Uniparental paternal disomy in a genetic cancer-predisposing syndrome. *Nature* 1991;**351**:665–7.
103 Mannens M, Hoovers JMN, Redeker B, *et al.* Parental imprinting of human chromosome region 11p15.3-pter involved in the Beckwith-Wiedemann syndrome and various human neoplasia. *Eur J Hum Genet* (submitted).
104 Nicholls RD, Knoll JHM, Butler MG, Karam S, Lalande M. Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome. *Nature* 1989;**342**:281–5.
105 Verga V, Hall BK, Wang S, *et al.* Localization of the translocation breakpoint in a female with Menkes syn-

drome to Xq13.2–q13.3 proximal to PGK-1. *Am J Hum Genet* 1991;**48**:1133–8.
106 Tümer Z, Tommerup N, Tønnesen T, *et al.* Mapping of the Menkes locus to Xq13.3 distal to the X-inactivation center by an intrachromosomal insertion of the segment Xq13.3–q21.2. *Hum Genet* 1992;**88**:668–72.
107 Tommerup N, Tümer Z, Tønnesen T, Horn N. A cytogenetic survey in Menkes disease. Implications for the detection of chromosomal rearrangements in X linked disorders. *J Med Genet* 1993;**30**:314–15.
108 Collins FA, Murphy DL, Reiss AL, *et al.* Clinical, biochemical, and neuropsychiatric evaluation of a patient with a contiguous gene syndrome due to a microdeletion Xp11.3 including the Norrie disease locus and monoamine oxidase (MAOA and MAOB) genes. *Am J Med Genet* 1992;**42**:127–34.
109 Lupski JR, Wise CA, Kuwano A, *et al.* Gene dosage is a mechanism for Charcot-Marie-Tooth disease type 1A. *Nature Genet* 1992;**1**:29–33.
110 Chamberlin J, Magenis RE. Parental origin of de novo chromosome rearrangements. *Hum Genet* 1980;**53**:343–7.
111 Chandley AC. On the parental origin of de novo mutation in man. *J Med Genet* 1991;**28**:217–23.
112 Ejima Y, Sasaki MS, Kaneko A, Tanooka H. Types, rates, origin and expressivity of chromosome mutations involving 13q14 in retinoblastoma patients. *Hum Genet* 1988;**79**:118–23.
113 Kean VM, MacLeod HL, Thompson MW, *et al.* Paternal inheritance of translocation chromosomes in a t(X;21) patient with X linked muscular dystrophy. *J Med Genet* 1986;**23**:491–3.
114 Bodrug SE, Roberson JR, Weiss L, *et al.* Prenatal identification of a girl with a t(X;4)(p21;q35) translocation: molecular characterisation, paternal origin, and association with muscular dystrophy. *J Med Genet* 1990;**27**:426–32.
115 Robinson D, Boyd Y, Collinson M, Jacobs P. Determination of the parental origin of X;autosome translocations by M27β methylation analysis. *J Med Genet* 1991;**28**:63–4.
116 Robinson DO, Boyd Y, Cockburn D, *et al.* The parental origin of de novo X-autosome translocations in females with Duchenne muscular dystrophy revealed by M27β methylation analysis. *Genet Res Camb* 1990;**56**:135–40.
117 Kapur S, Higgins JV, Delp K, Rogers B. Menkes syndrome in a girl with X-autosome translocation. *Am J Med Genet* 1987;**26**:503–10.
118 Bawle E, Tyrkus M, Lipman S, Bozimowski D. Aarskog syndrome: full male and female expression associated with an X-autosome translocation. *Am J Med Genet* 1984;**17**:595–602.
119 Kaffe S, Hsu LYF. Chromosome inversions in a series of 25.000 prenatal diagnoses: frequency and pregnancy outcome. *Am J Hum Genet* 1990;**47**:A278(1097).
120 Groupe de Cytogeneticiens Français. Pericentric inversions in man. A French collaborative study. *Ann Genet (Paris)* 1986;**29**:129–68.
121 Groupe de Cytogeneticiens Français. Paracentric inversions in man. A French collaborative study. *Ann Genet (Paris)* 1986;**29**:169–76.
122 Clayton-Smith J, Webb T, Pembrey ME, Nichols M, Malcolm S. Maternal origin of deletion 15q11–13 in 25/25 cases of Angelman syndrome. *Hum Genet* 1992;**88**:376–8.
123 Petersen MB, Frantzen M, Antonarakis SE, *et al.* Comparative study of microsatellite and cytogenetic markers for detecting the origin of the nondisjoined chromosome 21 in Down syndrome. *Am J Hum Genet* 1992;**51**:516–25.
124 Purvis-Smith SG, Saville T, Manass S, *et al.* Uniparental disomy 15 resulting from correction of an initial trisomy 15. *Am J Hum Genet* 1992;**50**:348–50.
125 Cassidy SB, Lai LW, Erickson RP, *et al.* Trisomy 15 with loss of paternal 15 as a cause of Prader-Willi syndrome due to maternal disomy. *Am J Hum Genet* 1992;**51**:701–8.
126 Norman AM, Read AP, Clayton-Smith J, Andrews T, Donnai D. Recurrent Wiedemann-Beckwith syndrome with inversion of chromosome (11)(p11.2p15.5). *Am J Med Genet* 1992;**42**:638–41.
127 Lüdecke HJ, Johnson C, Wagner MJ, *et al.* Molecular definition of the shortest region of deletion overlap in the Langer-Giedion syndrome. *Am J Hum Genet* 1991;**49**:1197–206.
128 Davis LM, Stallard R, Thomas GH, *et al.* Two anonymous DNA segments distinguish the Wilms' tumor and aniridia locus. *Science* 1988;**241**:840–2.
129 Bodrug SE, Ray PN, Gonzalez IL, *et al.* Molecular analysis of a constitutional X-autosome translocation in a female with muscular dystrophy. *Science* 1987;**237**:1620–4.
130 Bodrug SE, Burghes AH, Ray PN, Worton RG. Mapping of four translocation breakpoints within the Duchenne muscular dystrophy gene. *Genomics* 1989;**4**:101–4.
131 Meitinger T, Boyd Y, Anand R, Craig I. Mapping of Xp21 translocation breakpoints in and around the DMD gene by pulsed field gel electrophoresis. *Genomics* 1988;**3**:315–22.
132 Giacalone JP, Francke U. Common sequence motifs at the rearrangement sites of a constitutional X/autosome translocation and associated deletion. *Am J Hum Genet* 1992;**50**:725–41.
133 Higgins MJ, Hansen MF, Cavenee WK, Lalande M. Molecular detection of chromosomal translocations that disrupts the putative retinoblastoma susceptibility locus. *Mol Cell Biol* 1989;**9**:1–5.
134 Mitchell CD, Cowell JK. Predisposition to retinoblastoma due to a translocation within the 4.7R locus. *Oncogene* 1989;**4**:253–7.
135 Viskochil D, Buchberg AM, Xu G, *et al.* Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* 1990;**62**:187–92.
136 Cremers FPM, van de pol DJR, van Kerkhoff LPM, Wieringa B, Ropers HH. Cloning of a gene that is rearranged in patients with choroideraemia. *Nature* 1990;**347**:674–7.
137 Tsukamoto K, Tohma T, Ohta T, *et al.* Cloning and characterization of the inversion breakpoint at chromosome 2q35 in a patient with Waardenburg syndrome type I. *Hum Mol Genet* 1992;**1**:315–17.
138 Chelly J, Tümer Z, Tønnesen T, *et al.* Isolation of a candidate gene for Menkes disease that encodes for a potential heavy metal binding protein. *Nature Genet* 1993;**3**:14–19.
139 Stambolian D, Selleinger B, Derrington D, *et al.* Cytogenetic and molecular investigation of a balanced Xq13q translocation in a patient with retinoblastoma. *Am J Med Genet* 1992;**42**:771–6.
140 Happle R. Tentative assignment of hypomelanosis of Ito to 9q33-qter. *Hum Genet* 1987;**75**:98–9.
141 de Grouchy J, Turleau C, Doussau de Bazignan M, Maroteaux P, Thibaud D. Incontinentia pigmenti (IP) and r(X). Tentative mapping of the IP locus to the X juxtacentromeric region. *Ann Genet (Paris)* 1985;**28**:86–9.
142 Bernstein R, Dawson B, Kohl R, Jenkins T. X;15 translocation in a retarded girl: X inactivation pattern and attempt to localise the hexosaminidase A and other loci. *J Med Genet* 1979;**16**:254–62.
143 Gilgenkrantz S, Tridon P, Pinel-Briquel N, Beurey J, Weber M. Translocation (X;9)(p11;q34) in a girl with incontinentia pigmenti (IP): implications for the regional assignment of the IP locus to Xp11? *Ann Genet (Paris)* 1985;**28**:90–2.
144 Kajii T, Tsukahara M, Fukushima Y, *et al.* Translocation (X;13)(p11.21;q12.3) in a girl with incontinentia pigmenti and bilateral retinoblastoma. *Ann Genet (Paris)* 1985;**28**:219–23.
145 Hodgson SV, Neville B, Jones RWA, Fear C, Bobrow M. Two cases of X/autosome translocation in females with incontinentia pigmenti. *Hum Genet* 1985;**71**:231–4.
146 Cannizzaro LA, Hecht F. The gene for incontinentia pigmenti maps to band Xp11 with an (X;10)(p11;q22) translocation. *Clin Genet* 1987;**32**:66–9.
147 Bitoun P, Philippe C, Cherif M, Mulcahy MT, Gilgenkrantz S. Incontinentia pigmenti (type 1) and X;5-translocation. *Ann Genet (Paris)* 1992;**35**:51–4.
148 Sefiani A, Abel L, Heuertz S, *et al.* The gene for incontinentia pigmenti is assigned to Xq28. *Genomics* 1989;**4**:427–9.
149 Harris A, Lankester S, Haan E, *et al.* The gene for incontinentia pigmenti: failure of linkage studies using DNA probes to confirm cytogenetic localization. *Clin Genet* 1988;**34**:1–6.
150 Moss C, Burn J. Genetic counselling in hypomelanosis of Ito: case report and review. *Clin Genet* 1988;**34**:109–15.
151 Flannery DB. Pigmentary dysplasias, hypomelanosis of Ito, and genetic mosaicism. *Am J Med Genet* 1990;**35**:18–21.
152 Sefiani A, Heuertz S, Turleau C, *et al.* Incontinentia pigmenti: Xp breakpoint is not the same in a case of r(X) and in X/autosome translocations. *Ann Genet (Paris)* 1989;**32**:149–51.
153 Crolla JA, Gilgenkranz S, de Grouchy J, Kajii T, Bobrow M. Incontinentia pigmenti and X-autosome translocations. Non-isotopic in situ hybridization with an X-centromere specific probe (pSV2X5) reveals a possible X-centromeric breakpoint in one of five published cases. *Hum Genet* 1989;**81**:269–72.
154 Gorski JL, Burright EN, Reyner EL, *et al.* Isolation of DNA markers from a region between incontinentia pigmenti 1 (IP1) X-chromosomal translocation breakpoints by a comparative PCR analysis of a radiation hybrid subclone mapping panel. *Genomics* 1992;**14**:649–56.
155 Tommerup N, Lothe RA. Constitutional ring chromosomes and tumour suppressor genes. *J Med Genet* 1992;**29**:879–82.
156 Nisen P, Stamberg J, Ehrenpreis R, *et al.* The molecular basis of severe hemophilia B in a girl. *N Engl J Med* 1986;**315**:1139–42.
157 Journel H, Melki J, Turleau C, Munnich A, de Grouchy J. Rett phenotype with X/autosome translocation: possible mapping to the short arm of chromosome X. *Am J Med Genet* 1990;**35**:142–7.
158 Zoghbi HY, Ledbetter DH, Schultz R, Percy AK, Glaze DG. A de novo X;3 translocation in Rett syndrome. *Am J Med Genet* 1990;**35**:148–51.
159 Ellison KA, Fill CP, Terwilliger J, *et al.* Examination of X chromosome markers in Rett syndrome: exclusion mapping with a novel variation on multilocus linkage analysis. *Am J Hum Genet* 1992;**50**:278–87.
160 Tommerup N, Nielsen F. A familial reciprocal translocation t(3;7)(p21.1;p13) associated with the Greig polysyndactyly-craniofacial dysmorphism syndrome. *Am J Med Genet* 1983;**16**:313–21.
161 Krüger G, Götz J, Kvist U, *et al.* Greig syndrome in a large kindred due to reciprocal chromosome translocation t(6;7)(q27;p13). *Am J Med Genet* 1989;**32**:411–16.
162 Vortkamp A, Thias U, Gessler M, *et al.* A somatic cell hybrid panel and DNA probes for physical mapping of human chromosome 7p. *Genomics* 1991;**11**:737–43.
163 Wagner K, Kroisel PM, Rosenkranz W. Molecular and cytogenetic analysis in two patients with microdeletions

of 7p and Greig syndrome: hemizygosity for PGAM-2 and TCRG genes. *Genomics* 1990;**8**:487–91.
164 Pettigrew AL, Greenberg F, Caskey CT, Ledbetter DH. Greig syndrome associated with an interstitial deletion of 7p: confirmation of the localization of Greig syndrome to 7p13. *Hum Genet* 1991;**87**:452–6.
165 Brueton L, Huson SM, Winter RM, *et al.* Chromosomal localization of a developmental gene in man: direct DNA analysis demonstrates that Greig cephalopolysyndactyly maps to 7p13. *Am J Med Genet* 1988;**31**:799–804.
166 Vortkamp A, Gessler M, Grzeschik KH. GLI3 zinc-finger gene interrupted by translocations in Greig syndrome families. *Nature* 1991;**352**:539–40.
167 Wilson GN, Sauder SE, Bush M, Beitins IZ. Phenotypic delineation of ring chromosome 15 and Russell-Silver syndromes. *J Med Genet* 1985;**22**:237–40.
168 Yunis JJ, Ramsay NKC. Familial occurrence of the aniridia-Wilms' tumor syndrome with deletion 11p13–14.1. *J Pediatr* 1980;**96**:1027–30.
169 Kousseff BG, Agatucci A. Aniridia–Wilms tumor association. *J Pediatr* 1981;**98**:676–7.
170 Nakagome Y, Nagahara N. High-resolution studies in patients with aniridia-Wilms tumor association. *Hum Genet* 1985;**70**:289.
171 Cross I, Delhanty J, Chapman P, *et al.* An intrachromosomal insertion causing 5q22 deletion and familial adenomatous polyposis coli in two generations. *J Med Genet* 1992;**29**:175–9.
172 Williamson RA, Donlan MA, Dolan CR, *et al.* Familial insertional translocation of a portion of 3q into 11q resulting in duplication and deletion of region 3q22.1–q24 in different offspring. *Am J Med Genet* 1981;**9**:105–11.
173 Weissenbach J, Gyapay G, Dib C, *et al.* A second generation linkage map of the human genome. *Nature* 1992;**359**:794–801.
174 Schwartz M, Rosenberg T, Niebuhr E, *et al.* Choroideremia: further evidence for assignment of the locus to Xq13–Xq21. *Hum Genet* 1986;**74**:449–52.
175 Tabor A, Andersen O, Lundsteen C, Niebuhr E, Sardemann H. Interstitial deletion in the 'critical region' of the long arm of the X chromosome in a mentally retarded boy and his normal mother. *Hum Genet* 1983;**64**:196–9.
176 Chumakov I, Rigault P, Guillou S, *et al.* Continuum of overlapping clones spanning the entire human chromosome 21q. *Nature* 1992;**359**:380–7.
177 Foote S, Vollrath D, Hilton A, Page DC. The human Y chromosome: overlapping DNA clones spanning the euchromatic region. *Science* 1992;**258**:60–6.

Appendix This appendix contains references not mentioned in the text, listed alphabetically according to locus, including references to rearrangements included in tables 1 and 2, and some selected key references. Locus specific cross references to the text are included.

AGS Alagille syndrome
178 Anad F, Burn J, Matthews D, *et al.* Alagille syndrome and deletion of 20p. *J Med Genet* 1990;**27**:729–37.
179 Teebi AS, Krishna Murthy DS, Ismail EAR, Redha AA. Alagille syndrome with de novo del(20)(p11.2). *Am J Med Genet* 1992;**42**:35–8.
AHC Adrenal hypoplasia, congenital[72]
180 Pillers DAM, Weleber RG, Powell BR, *et al.* Åland Island eye disease (Forsius-Eriksson ocular albinism) and an Xp21 deletion in a patient with Duchenne muscular dystrophy, glycerol kinase deficiency, and congenital adrenal hypoplasia. *Am J Med Genet* 1990;**36**:23–8.
AIC Aicardi syndrome[70]
181 Naritomi K, Izumikawa Y, Nagataki S, *et al.* Combined Goltz and Aicardi syndromes in a terminal Xp deletion: are they a contiguous gene syndrome? *Am J Med Genet* 1992;**43**:839–43.
182 Ropers HH, Zuffardi O, Bianchi E, Tiepolo L. Agenesis of corpus callosum, ocular, and skeletal anomalies (X-linked dominant Aicardi's syndrome) in a girl with balanced X/3 translocation. *Hum Genet* 1982;**61**:364–8.
AIED Åland island eye disease[180]
ANCR Angelman syndrome (happy puppet)[65–69 122]
183 Williams CA, Zori RT, Stone JW, *et al.* Maternal origin of 15q11–13 deletions in Angelman syndrome suggests a role for genomic imprinting. *Am J Med Genet* 1990;**35**:350–3.
AN2 Aniridia 2[15 18 24 45–60 128 168–170]
ANK1 Spherocytosis type II (ankyrin defect)
184 Kimberling WJ, Fulbeck T, Dixon L, Lubs HA. Localization of spherocytosis to chromosome 8 or 12 and report of a family with spherocytosis and a reciprocal translocation. *Am J Hum Genet* 1975;**27**:586–94.
185 Bass EB, Smith SW Jr, Stevenson RE, Rosse WF. Further evidence for location of the spherocytosis gene on chromosome 8. *Ann Intern Med* 1983;**99**:192–3.
186 Chilcote RR, le Beau MM, Dampier C, *et al.* Association of red cell spherocytosis with deletion of the short arm of chromosome 8. *Blood* 1987;**69**:156–9.
187 Kitatani M, Chiyo M, Oxaki M, Shike S, Miwa S. Localization of the spherocytosis gene to chromosome segment 8p11.22–8p21. *Hum Genet* 1988;**78**:94–5.
188 Lux SE, Tse WT, Menninger JC, *et al.* Hereditary spherocytosis associated with deletion of human erythrocyte ankyrin gene on chromosome 8. *Nature* 1990;**345**:736–9.
APC Adenomatous polyposis coli, incl Gardner syndrome[171]
189 Herrera L, Kakati S, Gibas L, Pietrzak E, Sandberg AA. Gardner syndrome in a man with an interstitial deletion of 5q. *Am J Med Genet* 1986;**25**:473–6.
190 Hockey KA, Mulcahy MT, Montgomery P, Levitt S. Deletion of chromosome 5q and familial adenomatous polyposis. *J Med Genet* 1989;**26**:61–2.
191 Kobayashi T, Narahara K, Yokoyama Y, *et al.* Gardner syndrome in a boy with interstitial deletion of the long arm of chromosome 5. *Am J Med Genet* 1991;**41**:460–3.
192 Lindgren V, Bryke CR, Ozcelik T, Yang-Feng TL, Francke U. Phenotypic, cytogenetic, and molecular studies of three patients with constitutional deletions of chromosome 5 in the region of the gene for familial adenomatous polyposis. *Am J Hum Genet* 1992;**50**:988–97.
AZF Azoospermia
193 Anderson M, Page DC, Pettay D, *et al.* Y;autosome translocations and mosaicism in the aetiology of 45,X maleness: assignment of fertility factor to distal Yq11. *Hum Genet* 1988;**79**:2–7.
194 Bardoni B, Zuffardi O, Guioli S, *et al.* A deletion map of the human Yq11 region: implications for the evolution of the Y chromosome and tentative mapping of a locus involved in spermatogenesis. *Genomics* 1991;**11**:443–51.
195 Ma K, Sharkey A, Kirsch S, *et al.* Towards the molecular localisation of the AZF locus: mapping of microdeletions in azoospermic men within 14 subintervals of interval 6 of the human Y chromosome. *Hum Mol Genet* 1992;**1**:29–33.
196 Diaz-Castanos LR, Rivera H, Gonzales-Montes RM, Diaz M. Translocation (Y;19)(q12;q13) and azoospermia. *Ann Genet (Paris)* 1991;**34**:27–9.
BPES Blepharophimosis, ptosis, epicanthus inversus syndrome[172]
197 De Almeida JCC, Llerena JC Jr, Neto JBG. Another example favouring the location of BPES at 3q2. *J Med Genet* 1993;**30**:86.
198 De Die-Smulders CEM, Engelen JJM, Donk JM, Fryns JP. Further evidence for the location of the BPES gene at 3q2. *J Med Genet* 1991;**28**:725.
199 Fujita H, Meng J, Kawamura M, *et al.* Boy with a chromosome del(3)(q12q23) and blepharophimosis syndrome. *Am J Med Genet* 1992;**44**:434–6.
200 Fukushima Y, Wakui K, Nishida T, Ueoka Y. Blepharophimosis syndrome and a de novo balanced autosomal translocation [46,XY,t(3;4)(q23;p15.2)]. Possible location of blepharophimosis syndrome to 3q23. *Am J Hum Genet* 1990;**47**:A29.
201 Jewett T, Rao PN, Weaver RG, *et al.* Blepharophimosis syndrome (BPES) associated with del 3q22: gene assignment to the interphase of band 3q22–q23. *Am J Hum Genet* 1992;**51**(suppl):A81.
BWS Beckwith-Wiedemann syndrome[102 103 126]
202 Brown KW, Gardner A, Williams JC, *et al.* Paternal origin of 11p15 duplications in the Beckwith-Wiedemann syndrome. *Cancer Genet Cytogenet* 1992;**58**:55–70.
203 Haas OA, Zoubek A, Grumayer ER, Gadner H. Constitutional interstitial deletion of 11p11 and pericentric inversion of chromosome 9 in a patient with Wiedemann-Beckwith syndrome and hepatoblastoma. *Cancer Genet Cytogenet* 1986;**23**:95–104.
204 Pueschel SM, Padre-Mendoza T. Chromosome 11 and Beckwith-Wiedemann syndrome. *J Pediatr* 1984;**104**:484–5.
205 Schmutz SM. Deletion of chromosome 11(p11p13) in a patient with Beckwith-Wiedemann syndrome. *Clin Genet* 1986;**30**:154–6.
CDPX1 Chondrodysplasia punctata 1[70]
206 Ballabio A, Carrozzo R, Gil A, *et al.* Molecular characterization of human X/Y translocations suggests their aetiology through aberrant exchange between homologous sequences on Xq and Yq. *Ann Hum Genet* 1989;**53**:9–14.
CMPD1/SRA1 Campomelic dysplasia/sex reversal, autosomal 1[94–97 101]
CMT1A Charcot-Marie-Tooth neuropathy 1[109]
CRS1 Craniosynostosis, syndromic 1
207 Motegi T, Ohuchi M, Ohtaki C, *et al.* A craniosynostosis in a boy with a del(7) (p15.3p21.3): assignment by deletion mapping of the critical segment for craniosynostosis to the mid-portion of 7p21. *Hum Genet* 1985;**71**:160–2.
208 Speleman F, Craen M, Leroy J. De novo terminal deletion 7p22.1→pter in a child without craniosynostosis. *J Med Genet* 1989;**26**:528–32.
CYBB Chronic granulomatous disease
209 Royer-Pokora B, Kunkel LM, Monaco AP, *et al.* Cloning of the gene for an inherited human disorder—chronic granulomatous disease—on the basis of its chromosomal location. *Nature* 1986;**322**:32–8.
210 de Saint-Basile G, Bohler MC, Fischer A, *et al.* Xp21 DNA microdeletion in a patient with chronic granulomatous disease, retinitis pigmentosa, and McLeod phenotype. *Hum Genet* 1988;**80**:85–9.
DFN3 Deafness, conductive, with fixed stapes[271]
211 Reardon W, Roberts S, Phelps PD, *et al.* Phenotypic evidence for a common pathogenesis in X-linked deafness pedigrees and in Xq13–q21 deletion related deafness. *Am J Med Genet* 1992;**44**:513–17.
DGCR1 DiGeorge syndrome 1
212 Augusseau S, Jouk S, Jalbert P, Prieur M. DiGeorge syndrome and 22q11 rearrangements. *Hum Genet* 1986;**74**:206.
213 Carey AH, Roach S, Williamson R, *et al.* Localization of 27 DNA markers to the region of human chromosome 22q11-pter deleted in patients with the DiGeorge syndrome and duplicated in the der22 syndrome. *Genomics* 1990;7:299–306.

[214] Greenberg F, Elder FFB, Haffner P, Northrup H, Ledbetter DH. Cytogenetic findings in a prospective series of patients with DiGeorge anomaly. *Am J Hum Genet* 1988;**43**:605–11.
[215] Driscoll DA, Budarf ML, Emanuel BS. A genetic etiology for DiGeorge syndrome: consistent deletions and microdeletions of 22q11. *Am J Hum Genet* 1992;**50**:924–33.
[216] Scambler PJ, Carey AH, Wyse RKH, *et al.* Microdeletions within 22q11 associated with sporadic and familial DiGeorge syndrome. *Genomics* 1991;**10**:201–6.
[217] Wilson DI, Cross IE, Goodship JA, *et al.* A prospective cytogenetic study of 36 cases of DiGeorge syndrome. *Am J Hum Genet* 1992;**51**:957–63.
DGCR2 DiGeorge syndrome 2[214]
[218] Monaco G, Ciccimarra F, Pignata C, Garofalo S. T cell immunodeficiency in a patient with 10p deletion syndrome. *J Pediatr* 1989;**115**:330.
DMD/BMD Duchenne and Becker muscular dystrophy[1–5 71 72 75 113–116 129–132]
[219] Boyd Y, Buckle V, Holt S, *et al.* Muscular dystrophy in girls with X;autosome translocations. *J Med Genet* 1986;**23**:484–90.
[220] Boyd Y, Buckle VJ. Cytogenetic heterogeneity of translocations associated with Duchenne muscular dystrophy. *Clin Genet* 1986;**29**:108–15.
[221] Boyd Y, Cockburn D, Holt S, *et al.* Mapping of 12 translocation breakpoints in the Xp21 region with respect to the locus for Duchenne muscular dystrophy. *Cytogenet Cell Genet* 1988;**48**:28–34.
[222] Monaco AP, Neve RL, Coletti-Feener C, *et al.* Isolation of candidate cDNA for portions of the Duchenne muscular dystrophy gene. *Nature* 1986;**323**:646–50.
[223] Ray PN, Belfall B, Duff C, *et al.* Cloning of the breakpoint of an X;21 translocation associated with Duchenne muscular dystrophy. *Nature* 1985;**318**:672–5.
EDA Ectodermal dysplasia, anhidrotic (hypohidrotic)
[224] Limon J, Filipiuk J, Nedoszytko B, *et al.* X-linked anhidrotic ectodermal dysplasia and de novo t(X;1) in a female. *Hum Genet* 1991;**87**:338–40.
[225] MacDermot KD, Hultén M. Female with hypohidrotic ectodermal dysplasia and de novo (X;9) translocation. Clinical documentation of the AnLy cell line case. *Hum Genet* 1990;**84**:577–9.
[226] Plougastel B, Couillin P, Blanquet V, *et al.* Mapping around the Xq13.1 breakpoints of two X/A translocations in hypohidrotic ectodermal dysplasia (EDA) female patients. *Genomics* 1992;**14**:523–5.
[227] Turleau C, Niaudet P, Cabanis MO, *et al.* X-linked hypohidrotic ectodermal dysplasia and t(X;12) in a female. *Clin Genet* 1989;**35**:462–6.
[228] Zonana J, Roberts SH, Thomas NS, Harper PS. Recognition and reanalysis of a cell line from a manifesting female with X linked hypohidrotic ectodermal dysplasia and an X;autosome balanced translocation. *J Med Genet* 1988;**25**:383–6.
F9 Haemophilia B (coagulation factor IX deficiency)
[229] Vianna-Morgante AM, Batista DAS, Levisky RB, Zatz M. X;autosomal translocations in females with X-linked recessive diseases. *7th Int Congr Hum Genet (Berlin)* 1987;**I**:97.
FGDY Aarskog syndrome[118]
GCPS Greig cephalopolysyndactyly[160–166]
GFDH Goltz focal dermal hypoplasia[70]
GK Glycerol kinase deficiency[71 72]
[230] Walker AP, Muscatelli F, Monaco AP. Isolation of the human glycerol kinase gene by positional cloning. *Hum Mol Genet* 1993;**2**:107–14.
HLD Huntington-like disease
[231] Froster-Iskenius UG, Hayden MR, Wang HS, *et al.* A family with Huntington disease and reciprocal translocation 4;5. *Am J Hum Genet* 1986;**38**:759–67.
[232] Steele MW, Wenger SL, Chorazy A, *et al.* Chromosome site 4q21 and Huntington like disease (HLD). *Am J Hum Genet* 1987;**41**:A85.
HMRD Haemoglobin H disease/mental retardation (deletion type)[88]
HPE2 Holoprosencephaly 2
[233] Hecht BKM, Hecht F, Münke M. Forebrain cleavage gene causing holoprosencephaly: deletion mapping to chromosome band 2p21. *Am J Med Genet* 1991;**40**:130.
HPE3 Holoprosencephaly 3
[234] Münke M. Clinical, cytogenetic, and molecular approaches to the genetic heterogeneity of holoprosencephaly. *Am J Med Genet* 1989;**34**:237–45.
[235] Hatziioannou A, Krauss CM, Lewis MB, Halazonetis TD. Familial holoprosencephaly associated with a translocation breakpoint at chromosomal position 7q36. *Am J Med Genet* 1991;**40**:201–5.
[236] Lurie IW, Ilyina HG, Podleschuk LV, Gorelik LB, Zaletajev DV. Chromosome 7 abnormalities in parents of children with holoprosencephaly and hydronephrosis. *Am J Med Genet* 1990;**35**:286–8.
[237] Gurrieri F, Trask BJ, van den Engh G, *et al.* Physical mapping of the holoprosencephaly critical region in 7q36. *Nature Genet* 1993;**3**:247–51.
HPE4 Holoprosencephaly 4
[238] Cohen MM. Perspectives on holoprosencephaly. Part III. Spectra, continuities, and discontinuities. *Am J Med Genet* 1989;**35**:271–88.
HSCR Hirschsprung disease
[239] Bottani A, Xie Y, Binkert F, Schinzel A. A case of Hirschsprung disease with a chromosome 13 microdeletion, del(13)(q32.3q33.2): potential mapping of one disease locus. *Hum Genet* 1991;**87**:748–50.
[240] Lamont MA, Fitchett M, Dennis NR. Interstitial deletion of distal 13q associated with Hirschsprung's disease. *J Med Genet* 1989;**26**:100–4.
[241] Kiss P, Osztovics M. Association of 13q deletion and Hirschsprung's disease. *J Med Genet* 1989;**26**:793–6.
IDS Hunter disease (iduronate-2-sulphatase deficiency)
[242] le Guern E, Couillin P, Oberlé I, Ravise N, Boue J. More precise localization of the gene for Hunter syndrome. *Genomics* 1990;**7**:358–62.
[243] Mossman J, Blunt S, Stephen R, Jones EE, Pembrey M. Hunter's disease in a girl: association with X;5 chromosomal translocation disrupting the Hunter gene. *Arch Dis Child* 1986;**58**:911–15.
IP1 Incontinentia pigmenti 1[140–154]
KAL1 Kallmann syndrome 1[70]
LGCR Langer-Giedion syndrome[127]
[244] Bühler EM, Bühler UK, Beutler C, Fessler R. A final word on the tricho-rhino-phalangeal syndromes. *Clin Genet* 1987;**31**:273–5.
[245] Gorlin RJ, Cervenka J, Bloom BA, Langer LO Jr. No chromosome deletion found on prometaphase banding in two cases of Langer-Giedion syndrome. *Am J Med Genet* 1982;**13**:345–7.
[246] Ogle RF, Dalzell P, Turner G, Wass D, Yip MY. Multiple exostoses in a patient with t(8;11)(q24.11;p15.5). *J Med Genet* 1991;**28**:881–3.
[247] Shabtai F, Sandowski U, Nissimow R, Klar D, Halbrecht I. Familial syndrome with some features of the Langer-Giedion syndrome, and paracentric inversion of chromosome 8, inv 8 (q11.23–q21.1). *Clin Genet* 1985;**27**:600–5.
[248] Turleau C, Chavin-Colin F, de Grouchy J, *et al.* Langer-Giedion syndrome with and without del 8q: assignment of critical segment to 8q23. *Hum Genet* 1982;**62**:183–7.
LYP Lymphoproliferative syndrome, X linked[73]
MBS Moebius syndrome
[249] Slee JJ, Smart RD, Viljoen DL. Deletion of chromosome 13 in Moebius syndrome. *J Med Genet* 1991;**28**:413–14.
[250] Ziter FA, Wiser WC, Robinson A. Three generation pedigree of a Moebius syndrome variant with chromosome translocation. *Arch Neurol* 1977;**34**:437–42.
MDCR Miller-Dieker syndrome[10–12 25 26]
MNK Menkes disease[105–107]
[251] Mercer JFB, Livingstone J, Hall B, *et al.* Isolation of a partial candidate gene for Menkes disease by positional cloning. *Nature Genet* 1993;**3**:20–5.
[252] Vulpe C, Levinson B, Whitney S, Packman S, Gitschier J. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. *Nature Genet* 1993;**3**:7–13.
MRX2 Mental retardation, X linked[70]
NDP Norrie disease[108]
[253] Ohba N, Yamashita T. Primary vitreoretinal dysplasia resembling Norrie's disease in a female: association with X autosome chromosomal translocation. *Br J Ophthalmol* 1986;**70**:64–71.
[254] Pettenati MJ, Rao PN, Weaver RG Jr, Thomas IT, McMahan MR. Inversion (X)(p11.4q22) associated with Norrie disease in a four generation family. *Am J Med Genet* 1993;**45**:577–80.
NF1 Neurofibromatosis 1 (von Recklinghausen)[90–93 135]
NF2 Neurofibromatosis 2 (central, bilateral acoustic neurinoma)
[255] Arai E, Ikeuchi T, Karasawa S, *et al.* Constitutional translocation t(4;22)(q12;q12.2) associated with neurofibromatosis type 2. *Am J Med Genet* 1992;**44**:163–7.
OA1 Ocular albinism 1 (Nettleship-Falls type)[70]
OCRL Oculocerebrorenal syndrome of Lowe
[256] Hodgson SV, Heckmatt JZ, Hughes E, Crolla JA, Dubowitz V, Bobrow M. A balanced de novo X/autosome translocation in a girl with manifestations of Lowe syndrome. *Am J Med Genet* 1986;**23**:837–47.
[257] Mueller OT, Hartsfield JK Jr, Gallardo LA, *et al.* Lowe oculocerebrorenal syndrome in a female with a balanced X;20 translocation: mapping of the X chromosome breakpoint. *Am J Hum Genet* 1991;**49**:804–10.
PAX6 Paired box gene 6 associated with aniridia[19 24]
PBT Piebald trait
[258] Yamamoto Y, Nishimoto H, Ikemoto S. Interstitial deletion of the proximal long arm of chromosome 4 associated with father–child incompatibility within the Gc-system. Probable reduced gene dosage effect and partial piebald trait. *Am J Med Genet* 1989;**32**:520–3.
[259] Funderburk SJ, Crandall BF. Dominant piebald trait in a retarded child with a reciprocal translocation and small intercalary deletion. *Am J Hum Genet* 1974;**26**:715–22.
[260] Hoo JJ, Haslam RHA, van Orman C. Tentative assignment of piebald trait gene to chromosome band 4q12. *Hum Genet* 1986;**73**:230–1.
[261] Lacassie Y, Thurmon TF, Tracy MC, Pelias MZ. Piebald trait in a retarded child with interstitial deletion of chromosome 4. *Am J Hum Genet* 1977;**29**:641–2.
PWCR Prader-Willi syndrome[61–64 104 124 125]
RB1 Retinoblastoma susceptibility[38–44 112 133 134 139]
RP3 Retinitis pigmentosa 3
[262] McDowell C, Burghes AH, Anson-Cartwright S, *et al.* X-linked retinitis pigmentosa (XLRP): mapping of the gene to Xp21, pulsed field gel electrophoresis (PFGE) of the region and cloning strategies. *Am J Hum Genet* 1990;**47**:A256(1009).
RSTS Rubinstein-Taybi syndrome[84–87]
SHFD1 Split hand and foot deformity 1
[263] Hasegawa T, Hasegawa Y, Assamura S, *et al.* EEC syndrome (ectrodactyly, ectodermal dysplasia and cleft lip/palate) with a balanced reciprocal translocation between

7q11.21 and 9p12 (or 7p11.2 and 9q12). *Clin Genet* 1991;**40**:202–6.

[264] Qumsiyeh MB. EEC syndrome (ectrodactyly, ectodermal dysplasia and cleft lip/palate) is on 7p11.2–q21.3. *Clin Genet* 1992;**42**:101.

[265] Rivera H, Sanchez-Corona J, Burgos-Fuentes VR, Melendez-Ruiz MJ. Deletion of 7q22 and ectrodactyly. *Genet Counsel* 1992;**2**:27–31.

[266] Sharland M, Patton MA, Hill L. Ectrodactyly of hands and feet in a child with a complex translocation including 7q21.2. *Am J Med Genet* 1991;**39**:413–14.

SRY Testis-determining factor[70]

[267] Disteche CM, Casanova M, Saal H, *et al.* Small deletions of the short arm of the Y chromosome in 46,XY females. *Proc Natl Acad Sci USA* 1986;**83**:7841–4.

[268] Ferguson-Smith MA, Cooke A, Affara NA, Boyd E, Tolmie JL. Genotype–phenotype correlations in XX males and their bearing on current theories of sex determination. *Hum Genet* 1990;**84**:198–202.

[269] Sinclair AH, Berta P, Palmer MS, *et al.* A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* 1990;**346**:240–4.

SS Short stature, X linked[70]

[270] Ogata T, Matsuo N, Shimuzu N. A ring X chromosome, 46,Y,r(X)(p22.33q28), as a cause of extreme short stature in a male. *Am J Med Genet* 1990;**35**:241–4.

STS X linked ichthyosis[70]

TCD Choroideraemia[37 136 174 175]

[271] Cremers FP, Van den Pol DJR, Diergaarde PJ, *et al.* Physical fine mapping of the choroideremia locus using Xq21 deletions associated with complex syndromes. *Genomics* 1989;**4**:41–6.

[272] Kaplan J, Gilgenkrantz S, Dufier JL, Frézal J. Choroideremia and ovarian dysgenesis associated with an X;7 de novo balanced translocation (HGM10). *Cytogenet Cell Genet* 1989;**51**:1022.

[273] Merry DE, Jänne PA, Landers JE, Lewis RA, Nussbaum RL. Isolation of a candidate gene for choroideraemia. *Proc Natl Acad Sci USA* 1992;**89**:2135–9.

[274] Siu VM, Gonder JR, Jung JH, Sergovich FR, Flintoff WF. Choroideremia associated with an X-autosomal translocation. *Hum Genet* 1990;**84**:459–64.

TKC Torticollis, keloids, cryptorchidism, and renal dysplasia

[275] Zuffardi O, Fraccaro M. Gene mapping and serendipity. The locus for torticollis, keloids, cryptorchidism and renal dysplasia (31430, McKusick) is at Xq28, distal to the G6PD locus. *Hum Genet* 1982;**62**:280–1.

TRP1 Trichorhinophalangeal syndrome 1

[276] Fryns JP, Van den Berghe H. 8q24.12 interstitial deletion in trichorhinophalangeal syndrome type I. *Hum Genet* 1986;**74**:188–9.

[277] Goldblatt J, Smart RD. Tricho-rhino-phalangeal syndrome without exostoses, with an interstitial deletion of 8q23. *Clin Genet* 1986;**29**:434–8.

[278] Hamers A, Jongbloet P, Peeters G, Fryns JP, Geraedts J. Severe mental retardation in a patient with tricho-rhino-phalangeal syndrome type I and 8q deletion. *Eur J Pediatr* 1990;**149**:618–20.

[279] Naritomi K, Hirayama K. Partial trisomy of distal 8q derived from mother with mosaic 8q23.3–24.13 deletion, and relatively mild expression of tricho-rhinophalangeal syndrome I. *Hum Genet* 1989;**82**:199–201.

[280] Yamamoto Y, Oguro N, Miyao M, Yanagisawa M. Tricho-rhino-phalangeal syndrome type I with severe mental retardation due to interstitial deletion of 8q23.3–24.13. *Am J Med Genet* 1989;**32**:133–5.

[281] Haan EA, Hull YJ, White S, *et al.* Tricho-rhino-phalangeal and branchio-oto syndromes in a family with an inherited rearrangement of chromosome 8q. *Am J Med Genet* 1989;**32**:490–4.

VCFS Velo-cardio-facial syndrome

[282] Driscoll DA, Spinner NB, Budarf ML, *et al.* Deletions and microdeletions of 22q11.2 in velo-cardio-facial syndrome. *Am J Med Genet* 1992;**44**:261–8.

[283] Scambler PJ, Kelly D, Lindsay E, *et al.* Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *Lancet* 1992;**339**: 1138–9.

[284] Kelly D, Goldberg R, Wilson D, *et al.* Confirmation that the velo-cardio-facial syndrome is associated with haploinsufficiency of genes at chromosome 22q11. *Am J Med Genet* 1993;**45**:308–12.

VWS Van der Woude syndrome 1

[285] Bocian M, Walker AP. Lip pits and deletion 1q32–q41. *Am J Med Genet* 1987;**26**:437–43.

WAGR see also AN2, WT1[15]

[286] Puissant H, Azoulay M, Serre JL, Piet LL, Junien C. Molecular analysis of a reciprocal translocation t(5;11)(q11;p13) in a WAGR patient. *Hum Genet* 1988;**79**:280–2.

WS1 Wardenburg syndrome 1[137]

[287] Ishikiriyama S, Tonoki H, Shibuya Y, *et al.* Wardenburg syndrome type I in a child with a de novo inversion (2)(q35q37.3). *Am J Med Genet* 1989;**33**:505–7.

WT1 Wilms's tumour susceptibility[15–17 20–23 45–49 52–57 128 168–170 286]

XK Kell blood group precursor (McLeod phenotype)

[288] Ho MF, Monaco AP, Blonden LAJ, *et al.* Fine mapping of the McLeod locus (XK) to a 150–380-kb region in Xp21. *Am J Hum Genet* 1992;**50**:317–30.

ZWS Zellweger syndrome[30 31]